Name: Catalanotto, Frank

Address: 10302 SWrd Avene, Gainesville, Florida, 32607

Email: frankdentaltherapy@gmail.com

Board Name: Health Care Advisory Board

Primary Phone:

352-256-5909

Please list any civic and professional accomplishments/honors, training or experience related to this appointment::

Professor at UF College of Dentistry, Founder and President of of Floridians for Dental Access, numerous grants and publicationss on access to dental care

Please list any current/previous Advisory Board appointments:

Alachua County Health Care Advisory Board

What Contributions do you feel you could make if you were selected to this board?:

Good knowledge of access to dental care issues.

Please Agree with the following statements:

I understand this application is the property of Alachua County and subject to public records laws. I hereby certify that the statements made on this application are true and correct. I understand that Appointees to advisory board/committees are required to attend scheduled meetings as specified in the "Guidelines for Citizen Advisory Boards and Committees". I understand that some boards and committees require Financial Disclosure (Chapter 112, Florida Statutes) and I am willing to file if required. I affirm that my personal and business (if applicable) affairs within Alachua County are in substantial compliance with all county regulatory and taxing authorities rules and regulations?:

Yes

Employer :

University of Florida College of Dentistry

Occupation:

Professor

Are you currently serving, or have you ever served, on an Alachua County advisory board? :

Yes

If yes, please list board(s):

Health Care Advisory Board

Time of Submission: 02/20/24 12:29:56 PM

Attachments

- CV6.8.2021.pdf

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2000 Galloping Hill Road
Kenilworth, NJ 07033

TITLE:
PRevalence of Oral hpv infection, a Global aSSessment. The PROGRESS study

Protocol version	V2_A3
Protocol date	25 Sep 2020

Summary of Changes

Summary of Changes for Amendment 3.1

Protocol Section	***Change***
List of Abbreviations	GCP removed
6.1 Study Procedures	GCP removed

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Sponsor Contact Information

Smita Kothari
CORE, Executive Director
Merck & Co., Inc.
2000 Galloping Hill Road
Kenilworth, NJ 07033 USA

Edith Morais
CORE, Director
MSD
162 avenue Jean Jaurès
69007 Lyon – France
Tel. + 33 778 391 750

Taylor Gandy
CORE, Study Manager
Merck & Co., Inc.
2000 Galloping Hill Road
Kenilworth, NJ 07033 USA

Supplier Contact Information

Núria Lara
Senior Principal. Real World Evidence Solutions
C/ Provença 392, 3rd floor. 08025 Barcelona. Spain
Tel. +34 637 713 271

Montse Roset
Engagement Manager. Real World Evidence Solutions
C/ Provença 392, 3rd floor. 08025 Barcelona. Spain
Tel. +34 671 663 430

Montse Pedrós
Senior Consultant. Real World Evidence Solutions
C/ Provença 392, 3rd floor. 08025 Barcelona. Spain
Tel. +34 677 593 305

List of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Confidence Interval
CSRM	Clinical Safety and Risk Management
eCRF	Electronic Case Report Form
ERC	Ethics Review Committee
GP	General Practitioners
GPP	Good Pharmacoepidemiology Practices
HOIs	Health Outcomes of Interest
HPV	Human Papillomavirus
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Market Authorization Holder
MAR	Missing at Random
MCAR	Missing Not Completely at Random
NSAR	Non-Serious Adverse Reaction
ORG	Oral Rinse and Gargle
P25	Percentile 25
P50	Percentile 50
PCP	Primary Care Physicians
PQC	Product Quality Complaint
RMST	Risk Management Safety Team
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
STD	Sexually Transmittable Diseases
WHO	World Health Organization

Protocol Summary

Title	PRevalence of Oral hpv infection, a Global aSSessment. The PROGRESS Study
Supplier/Collaborator	IQVIA
Rationale	HPV is a sexually transmittable infection that can potentially self-resolve or cause anogenital and head and neck carcinomas. More than 200 genotypes of HPV have been identified; some are low-risk and some are high-risk, and may cause cancers such as cervical, vaginal, vulvar, anal, or head and neck cancers. HPV is a common infection in the general population. Recent data estimates the prevalence of oral HPV infection in 6.5% in Europe, 5.1% in the US, and 0.6% in Japan. Although the epidemiological data is limited, and based mostly on single-institution, cross-sectional studies and literature reviews. Some risk factors for HPV-positive head and neck carcinomas reported in the literature are a high number of oral sexual partners, tobacco use, and previous exposure to radiation. The information on oral HPV prevalence is limited across the world, and some aspects of the natural history of the HPV-related head and neck disease are still uncertain, with data gaps in the literature. Complementary data are needed for future surveillance on head and neck cancers and modelling studies. This study aims to gather more information on the natural history of the oral HPV infection in the general population in France, Germany, Italy, Spain, the United Kingdom, Japan and the United States. Additional countries might be added in a second phase.
Primary Objectives	To describe the natural history of the oral HPV infection in terms of its prevalence in general population, at overall level and by genotype. Additionally, in the US, to describe the incidence, persistence and clearance of oral HPV infection in the general population overall and by genotype.
Study Design	A non-interventional, cross-sectional study of subjects visiting the dentist for a regular check-up in the countries included in the study, with a prospective follow-up in the US
Study Population	Adult subjects visiting the dental clinic for a routine dental/oral examination (18-60 years old), not actively seeking health care due to any lesion in the oropharyngeal mucosa, which may be caused by HPV.
Study Duration	First subject first visit (estimated): November 2020 Last subject first visit/last subject in, all countries (estimated): December 2021 Last subject last visit, in the US (estimated): July 2023. In the US, each subject will be followed-up for up to 24 months.
Exposure and Outcome	Not applicable.
Statistical Methods	No hypothesis will be tested. Only descriptive statistics will be used to describe continuous and categorical variables. Missing variables will not be imputed.

Sample Size and Power Calculations[o]	The sample size required in each country has been calculated based on the estimations of prevalence of oral HPV infection of 6.5% (95% CI: 3.4-10.5) in Europe, 11.5% (95% CI: 9.8%−13.1%) in males and 3.2% (95% CI: 2.7%−3.8%) in females in the US, 0.67% (95% CI: 0.47%-0.93%) to 2.5% (95% CI: 1.8%-3.5%) in Asian countries. A total sample of 9,956 subjects, 2,968 subjects from the US, 1,164 subjects from each European country, and 1,168 subjects from Japan will allow to estimate the prevalence of HPV infection with acceptable precision levels (ranging from 0.7 to 2.6, depending on the prevalence). In the US, the sample of 2,968 subjects will allow estimating the HPV incidence in males (estimated between 4.4 and 5.6 cases per 100 subjects/year) and in females (estimated between 1.5 and 2.8 cases per 100 subjects/year) with a precision between 0.9% and 1.0% in males and between 0.5% and 0.7% in females. In addition, the sample size will allow to estimate the persistence rate at 6 months (estimated in 50%) with a precision of 7.3%.
Limitations	Representativeness of the general population is a critical point. In Italy, Spain and the US, the majority of participating dentists might be from private clinics, due to the high concentration of routine dental/oral examinations in these clinics. This site selection approach may select a biased sample of subjects with higher economical level than the general population. Prior studies have approached dental clinics for subject selection to estimate HPV prevalence among the general population. Other study limitations are based on the selection bias based on the sexual risk behavior and the challenge of collecting the information on the subjects' vaccination status.

1 Background and Rationale

1.1 Background

Human Papillomavirus (HPV) is a sexually transmittable infection that can potentially self-resolve or cause condyloma acuminata and can evolve into carcinoma in the genital area or in the head and neck area. More than 200 genotypes of HPV have been identified and more than 40 genotypes can affect the genital and/or the head and neck areas; some cause persistent infections leading to cancer development. HPV genotypes are classified as high or low-risk based on their oncogenic potential for cervical cancer[1].

According to recently published data, the prevalence of oral HPV infection, any type, in the general population in Europe and the United States (US) is 7.7%[2], slightly higher than the prevalence estimated by previous studies where it ranged between 2.4% and 6.9%, with a higher prevalence among men (3.2-11.5%) than among women (1.7-4%)[3,4,5,6,7,8,9]. While a meta-analysis including prevalence studies on oral HPV in healthy subjects worldwide found that the prevalence for males and females was similar, but in North America men had double risk of oral HPV infection compared to women[10]. The prevalence in Asian countries is lower with positive HPV tests in 0.6% to 0.8% among the general population in China[11,12]. In Japan, the data is scarce, in 2004 the prevalence of oral HPV among general population was estimated in 0.6%[13]. A study conducted in 2011 among female sex workers estimated a prevalence of 6.1% for oral HPV positivity[14]. According to age groups, the higher prevalence is seen in the 45-59 years old group where 8.7% of subjects were HPV positive, with the group aged 20-29 having the lowest prevalence, 6.2%[15], similarly a metanalysis reported prevalence increasing with age[10].

The estimated prevalence for any high-risk HPV type for the oral infection ranges between 1.2% and 3.7%. For or low-risk types, the prevalence ranges between 1.2% and 3.1%[5,6,8,16]. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 are of high-risk and recognized as oncogenic by the International Agency for Research on Cancer[17]. HPV 16 is the most frequent type[4] and its prevalence is estimated to be higher in elder groups, (1.4% and 1.3% among subjects between 45-59 and 60-69 years old, respectively) compared to younger groups (0.9% among subjects between 20-29 and 30-44 years old)[15]. In the US, the prevalence of oral HPV 16 was estimated in 1% by the National Health and Nutrition Examination Survey (NHANES) 2009–2010[3].

A recently published systematic review demonstrated that the prevalence and incidence of oral HPV infection due to any type, was lower than the prevalence and incidence of genital infection in the general population. This study estimated a prevalence of 1.4% and an incidence of 1.10 cases per 100 person-year for high-risk HPV 16[2]. Another study among patients with oropharyngeal squamous cell carcinoma estimated 71.1% of patients were infected with at least one high-risk genotype of HPV, and 3.9% were positive for two or more genotypes of HPV[18]. The incidence of oral HPV infection was estimated to be of 5.7 to 6.7 per 100 person-years in men and 6.8–39.6 per 100 person-years in women[19]. In the US, fewer data is available on the incidence of the oral HPV infection in general population. A recent study, the HPV in men or HIM study, conducted among men in the US, Brazil and Mexico reported an incidence of 4.4% (3.5-5.6) per year (95% CI)[20].

Several factors for HPV-positive head and neck carcinoma have been described in the literature. The most common risk factors are a high number of oral sexual partners, sexual behavior, tobacco use, alcohol use, history of exposure to radiation, and immunosuppression[21,22,23].

Nowadays, there is no curative treatment for the oral HPV infection; most of the infections are asymptomatic and self-resolve within two years[24]. Recent study results suggest that vaccination

against the HPV may sharply reduce oral HPV infections that are a major risk factor for oropharyngeal cancer, a type of head and neck cancer. In Europe, HPV vaccination coverage among female adolescents is highly variable across countries, ranging from 14.1% in Bulgaria and 19.1% in France, up to 80.0% in Sweden and 85.9% in the United Kingdom (UK)[25]. In the US, the vaccination coverage among adolescents between 13 and 17 years-old is 48.6%[26].

1.2 Rationale

The epidemiological data on the prevalence of the oral HPV infection currently available is based on single-institution[8,27,28] or cross-sectional studies[3,9,29] and a few literature reviews[19,30]. Therefore, the present study aims to assess prevalence in France, Germany, Italy, Spain, the UK, and Japan by detecting HPV DNA in oral rinse and gargle (ORG) samples overall and by genotype at a single timepoint, and for the US, at various timepoints.

It is important to understand the significant difference in oral HPV prevalence between men and women, since it has been reported to be disproportionately higher among men in some studies[9,20,31], but not confirmed by Mena et al in a meta-analysis of the prevalence worldwide[10]. Men are also at greater risk of oral HPV infection persistence than women[32]. Although, HPV vaccines are marketed in Europe and the US since 2006, the World Health Organization (WHO) recommends its use in girls among general population in their guidelines to cervical cancer control[33]. In most countries worldwide where vaccination programs for females have been established, the prevalence of the anogenital infection is decreasing with the HPV genotypes included in the vaccine for HPV[34] in the vaccinated cohorts[34,35,36]. More recently, vaccination of boys was also recommended in some countries across the world such as the US, Australia, Canada, Italy, Germany and in the UK.

Although none of the marketed vaccines are indicated for the prevention of the oral HPV infection, the prevalence of oral infection is decreasing in young people who are vaccinated for those HPV genotypes included in the vaccine compared to non-vaccinated[35].

In order to execute gender neutral programs, understanding the natural history of oral HPV infection and determining prevalence of oral HPV in a healthy population is imminent. This study will help identify those factors associated with the natural history of oral HPV infection, while understanding head and neck cancers, in order to predict the impact of HPV vaccination. Furthermore, additional data is needed for surveillance systems that can monitor oral HPV infection and HPV-attribution rates in HPV-related head and neck cancers and baseline data for modelling studies.

Increased prevalence of oral HPV infection and HPV-related oropharyngeal cancer in men can be attributed to higher HPV acquisition and slower clearance[29]. However, there are concerns across the methodology used in studies aiming to assess clearance and persistence of the HPV infection[2].

This study uses a standardized approach for epidemiological studies and aims to fill in the gaps expressed by Tam et al[2] and Kreimer et al[20] to gather information on the natural history of the HPV infection in the oral/oropharyngeal region among general healthy population in France, Germany, Italy, Spain, the UK, Japan and the US.

2 Objectives and Hypotheses

This is an epidemiological/observational study and does not test any hypotheses.

2.1 Primary Objective

The primary study objective is to assess the natural history of the oral HPV infection based on:

- Prevalence, as the detection of HPV DNA in ORG samples at the baseline visit, overall and by genotype.
- Additional primary objectives, only in the US:
  - Incidence: as the detection of HPV DNA in ORG samples at any follow-up visit after a negative test in the baseline/previous visits, overall and by genotype.
  - Persistence: as the detection of the same HPV genotype in ORG samples at two consecutive follow-up visits, following a positive test in the baseline/previous visits, overall and by genotype.
  - Clearance: as the lack of a positive of any HPV genotype in ORG samples at two consecutive follow-up visits, following a positive test in the baseline/previous visits overall and by genotype.

2.2 Secondary Objectives

Secondary objective is:

- To describe oral HPV infection risk factors, including demographic and sexual behavioral data.

3 METHODOLOGY

3.1 Summary of Study Design

- A non-interventional, cross-sectional study of subjects visiting the dentist for a regular check-up in France, Germany, Italy, Spain, UK and Japan, with a prospective follow-up in the US.
  - Approximately 17 sites/dentist clinics will participate in each European country and Japan. In the US, there will be about 44 sites. Each site is expected to include a maximum of 69 subjects who meet the inclusion and exclusion criteria as described in **Table 1**. A total of 1,164 subjects are expected to be recruited in each European country (including a total of 17 sites: 9 sites with 69 subjects and 8 sites with 68 subjects), 2,968 in the US (including a total of 44 sites: 24 sites with 67 subjects and 20 sites with 68 subjects), and 1,168 in Japan (including a total of 17 sites: 12 sites with 69 subjects and 5 sites with 68 subjects). See section 3.2. Site Recruitment and Site Initiation

Table 1 Distribution of study population among countries

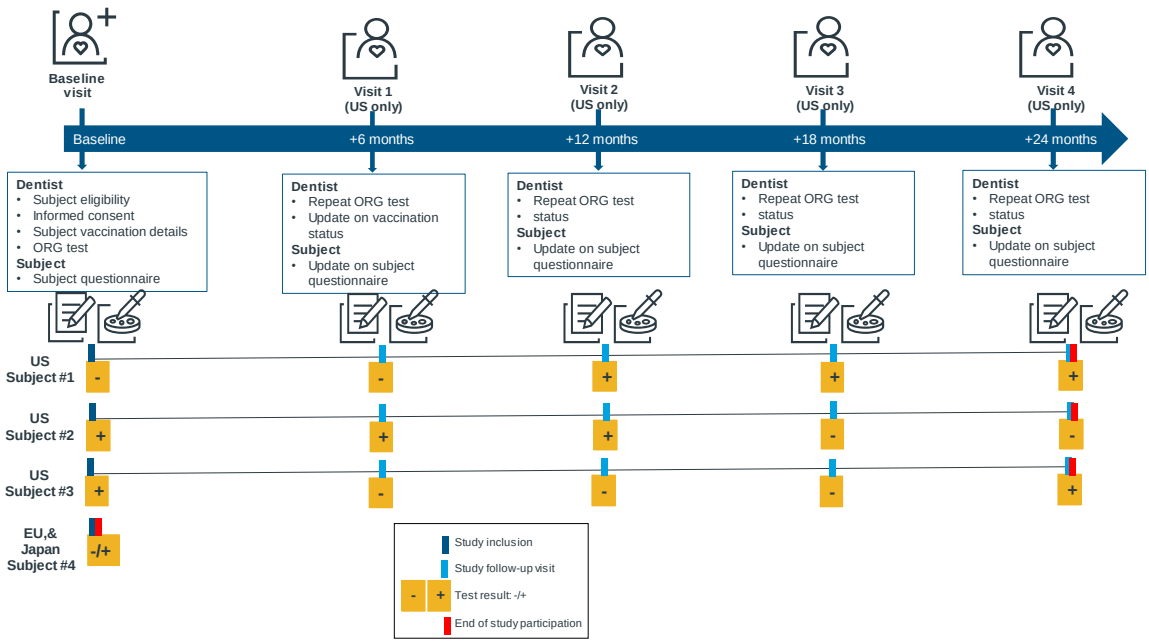
Countries	France	Germany	Italy	Spain	UK	Japan	US	Total
Dental clinics to participate	17	17	17	17	17	17	44	**163**
Expected number of subjects per clinic	9 sites: 69 8 sites :68	9 sites: 69 8 sites: 68	9 sites: 69 8 sites: 68	9 sites: 69 8 sites: 68	9 sites: 69 8 sites: 68	12 sites:69 5 sites:68	24 sites: 67 20 sites: 68	
Expected final sample per country	1,164	1,164	1,164	1,164	1,164	1,168	2,968	**9,956**

A random population of subjects visiting dental clinics in the participating countries who meet the inclusion and exclusion criteria will be recruited. The recruitment period may be a maximum of 40 consecutive working days per clinic. See section 3.3 Study Population for detailed subject recruitment procedures.

During the baseline visit, the dentist will assess the subject eligibility and will invite the subject to participate if they meet the inclusion/exclusion criteria, only after providing the subject information sheet. After obtaining the subject written informed consent, participating subjects will be asked to complete a subject questionnaire including sociodemographic, general clinical information, and behavior linked to the presence of oral HPV (smoking habits, alcohol consumption, sexual behavior). The dentist will collect some general and oral health information as well as the subject HPV vaccination status and details of the vaccine received, if vaccinated. See section 5 for detailed subject flow during the study visits. After survey completion, the dentist will collect an oral rinse and gargle (ORG) sample using the study test kits that will be provided (See appendix for further information on sample collection, storage and management) and will perform the visit following the clinical practice.

In the US, all subjects will be asked to come back every 6 months, with a final visit at 24 months, after the inclusion. During each follow-up visit, the subject will complete a questionnaire to update their sexual behavior, if it has changed since the last study visit. In all the follow-up visits, the sequence of surveys and tests will be always the same, starting with the questionnaire, following with the obtention of the ORG and the dental visit.

Figure 1: Study design



3.2. Site Recruitment and Site Initiation

The sites to be recruited for the study are dentist clinics and offices based in the participating countries. In some countries, additional healthcare providers may be involved. Dentists have been selected as the best healthcare provider that regularly see subjects from the general population with no major health issues (see section 8.2.2 Limitations).

Dental healthcare in participating countries may be distributed among public and private clinics.

All dentists that are working in a public and/or a private clinic (depending on the country) will be invited to complete a feasibility survey. This feasibility survey will be accessible through the Internet. It will assess the potential number of subjects each site could provide, the adequacy of facilities as per the study requirements and the willingness to participate. Each dentist will be allowed to respond once to the survey. The participating dentists will be selected from those responding to the feasibility survey, who want to take part in this non-interventional study and are spread across the country.

Selected dentists will be formally invited and to confirm willingness to participate. For those sites requiring approval by a specific Ethics Committee (EC), the procedures will start as soon as participation confirmation is received.

As soon as the EC approval is confirmed for each site, the startup activities will start with a remote site initiation meeting. All participating dentists and site collaborators (dentist, dentist nurse and any site staff involved in the study) will attend to a remote site initiation meeting before subject recruitment starts. During the site initiation meeting, the site monitor will train the dentist and any collaborator on the study protocol, study procedures and data collection; additionally, all the study documents will be shared. At the end of the meeting, each person involved in the study will receive their personal credentials for the study electronic Case Report Form (eCRF).

After receiving the study documents and credentials, the study monitor will activate the site and they will be able to start subject recruitment.

3.3 Study Population

This study will be conducted in France, Germany, Italy, Spain, the UK, Japan and the US. In subsequent steps, it is expected to expand the study to other countries and regions to assess the natural history of HPV oral infection, including HPV oral prevalence data only.

Table 2 presents the approximate number of subjects to be recruited by age and gender per each participating site to ensure an equal distribution of the subjects recruited among each gender and age group. In case that a site is not able to recruit some of the expected patients, a competitive recruitment in the country may be opened allowing the rest of the sites to recruit additional subjects in order to meet the planned sample size.

Table 2 Number of subjects to be recruited per site by age and gender

Gender/age group	France	Germany	Italy	Spain	UK	Japan	US
Males							
18 – 30 years	8	8	8	8	8	8	8
31 – 40 years	9	9	9	9	9	9	8
41 – 50 years	9	9	9	9	9	9	8
51 – 60 years	8	8	8	8	8	8	8
Total males	***34***	***34***	***34***	***34***	***34***	***34***	***32***
Females							
18 – 30 years	8	8	8	8	8	8	9
31 – 40 years	9	9	9	9	9	9	9
41 – 50 years	9	9	9	9	9	9	9
51 – 60 years	8	8	8	8	8	8	9
Total females	***34***	***34***	***34***	***34***	***34***	***34***	***36***
Total subjects per site	**68**	**68**	**68**	**68**	**68**	**68**	**68**

3.4 Inclusion Criteria

All inclusion and exclusion criteria will be reviewed by the dentist or qualified designee, in order to ensure that the subject qualifies for the study.

Subjects must meet all the following inclusion criteria to be eligible for inclusion in the study:

- ≥18 years old and ≤60 years old
- Subjects visiting the dental clinic for a routine dental/oral examination.
- Literate subjects who are able to comprehend and answer to the subject's questionnaires.
- Subjects who provide written informed consent.
- [Only in the US] Subjects are available for follow-ups for a maximum of 24 months.

3.5 Exclusion Criteria

Subjects must meet none of the following exclusion criteria to be eligible:

- Males and females >60 years old.
- Subjects visiting to the dentist with a diagnosis or suspicion of oral and/or oropharynx cancer.
- Subjects that received vaccination for HPV who are not recruited in France, Germany, Italy, Spain, UK, US and Japan.

4 Variables and Epidemiological Measurements

4.1 Variables

4.1.1. Variables reported by the dentist at baseline

- Dental clinic data
    - Type of clinic: private, public.
- Subject and oral health data
    - Age.
    - Gender.
    - General health of the oral cavity, including gingivitis and periodontitis.
    - Number of natural teeth missing/teeth issues.
    - Reason for the visit (looking for advice/routine check-up/pain or trouble in the oral cavity/treatment follow-up).
- HPV vaccination status:
    - Not vaccinated.
    - Vaccinated: age at vaccination, type of vaccine received and number of doses administered, dates of administrations (if available).

4.1.2. Variables collected in the subject questionnaire at baseline

A. Sociodemographic and clinical data

- Sociodemographic information: years of school, marital status, employment status.
- Healthcare and dental care insurance, including out-of-pocket and reimbursable expenses Dental care: frequency of dental brushing, use of mouthwash.
- Tonsillectomy.
- Smoking habits: cigarettes or other forms of tobacco, mean number of cigarettes per day and number of years smoking and number of years since smoking quit for ex-smokers.
- Alcohol consumption: frequency and quantity.
- Medical history: concomitant diseases and Sexually Transmittable Diseases (STDs).
- Weakened immune system due to any disease or treatment (i.e. HIV/AIDS infection, use of immune system-suppressing drugs after organ transplant, etc.).

B. Sexual behavior

The subject questionnaire will be based on questionnaires previously used to assess the subject sexual behavior in observational[29] and interventional[20] studies to assess oral HPV infection. The questionnaire will include the following variables:

- Sexual orientation: sex with men, sex with women, both.

- Sexual activity: if no, no further questions will be completed.
    - Age at first sexual intercourse.
    - Number of lifetime and last year sexual partners (men and women).
    - Oral sexual activity: if yes:
        - Age at first oral sex.
        - Number of lifetime and last year oral sex partners (men and women).
        - Last time any/oral sex.
        - Sexual partners with genital warts: if yes, number.

4.1.3. Variables to be confirmed through a telephone call after the dentist visit

- HPV vaccination status:
    - Not vaccinated.
    - Vaccinated: age at vaccination, type of vaccine received, and number of doses administered, dates of administrations (if available).

4.1.4. Variables collected by the dentist at the follow-up visits at follow-up visits in the US

- General health of the oral cavity, including gingivitis and periodontitis.
- Number of natural teeth missing/teeth issues.
- Change in HPV vaccination status since last study visit. If yes, dentist asks for the information
    - Type of vaccine received, and number of doses administered, dates of administrations (if available).

4.1.5. Variables collected in the subject questionnaire at follow-up visits in the US

A. Sociodemographic and clinical data

- Changes in demographic information.
- Smoking habits:
    - Change in smoking habits, if it has changed since last study visit. If no, skip this question.
    - Type of tobacco product used, mean number of cigarettes per day and number of years smoking, and number of years since smoking quit for ex-smokers.
- Alcohol consumption:
    - Change on alcohol consumption since last study visit. If no, skip this question.
    - Current frequency and quantity.
- Medical history:
    - Newly diagnosed concomitant diseases and Sexually Transmittable Diseases (STDs) since last study visit. If no, skip this question.

- Newly diagnosed weakened immune system due to any disease or treatment (i.e. HIV/AIDS infection, use of immune system-suppressing drugs after organ transplant, etc.). If no, skip this question.

B. Sexual behavior since last study visit (approx. 6 months ago)

- Sexual activity. If no, move to section C.
  - Number of new sexual partners (men and women).
  - Oral sexual activity: if yes:
    - Number of new oral sex partners (men and women).
    - Last time any/oral sex.
    - New sexual partners with genital warts: if yes, number.

4.1.5. Laboratory data reported by a centralized laboratory

- Test result: positive, negative. For all positive tests:
  - HPV DNA
  - HPV genotype

5 Subject Recruitment and Study Flow Chart

In order to recruit a random population and minimize selection bias, each dentist will consider the first 5 consecutive subjects who attend to the dental clinic each day for a period of 17 consecutive working days for participation. Those subjects between 18 and 60 years old attending the dental clinic fulfilling the inclusion/exclusion criteria but are not willing to participate will be registered in a subject log with their age and gender. The subjects accepting participation will be assigned a consecutive ID number, which will be the subject study number to be used across all the study documents.

In the case that the number of eligible subjects is lower than 5 per day, the recruitment period can be extended up to a maximum of 40 consecutive working days, or until the dentist recruits 68-69 subjects who have the required demographic characteristics, whichever comes first.

All subjects accepting to participate will be asked to provide written informed consent. After obtaining the subjects' written informed consent, the dentist will handle the subject questionnaire to be completed. Once the questionnaire is completed, the subject will be asked to place it in a closed envelope, The dentist or collaborator involved in the study will collect the envelope and confirm that it has the corresponding subject ID number and keep them in a lock cabinet.

In the US, the subject questionnaire will be available online, accessible through Internet from a computer, tablet or a cell phone. The investigator will provide the subject with the link or the QR code to access the questionnaire and allow the subject to complete it privately.

Once the questionnaire is collected, the dentist will collect the ORG as detailed in Section 12.1 ORG test, before conducting any other procedures on the subject.

Within the week following the study baseline visit, the dentist or collaborator will contact all the subjects that consented to receiving the call, to confirm the vaccination status and details previously provided, when available.

In the US, after the baseline visit, all the subjects will be asked to come back every 6 months (+/- 4 weeks), with the final visit occurring a maximum of 24 months (+/- 4 weeks) after baseline. In the US, two checkups per calendar year are recommended (every 6 months (+/- 3 months) and the study follow-up visits will be aligned to this regular practice. The objective of the follow-up visits is to assess the incidence, persistence and clearance of oral HPV infection.

In the US, before each follow-up visit, the dentist or collaborator will call the subject to schedule an appointment within the visit window period. The day of the visit, the subject will complete the subject follow-up questionnaire, also accessible online. After the completion of the questionnaire, the dentist will collect the ORG before conducting any other procedure on the subject.

Table 3 Study flow chart

Study Period:	**Study visits**				
Visit Number	**Baseline (all countries)**	**Visit #1 (only US)**	**Visit #2 (only US)**	**Visit #3 (only US)**	**Visit #4 (only US)**
Study Week/Month	0	6 months	12 months	18 months	24 months
Study Window, Weeks	0	4	4	4	4
Inclusion/Exclusion Criteria	X				
Informed Consent	X				
ORG test performance	X	X	X	X	X
Dentist-reported variables					
• *Sociodemographic*	X				
• *Oral health status*	X	X	X	X	X
• *HPV vaccination status*	X	X*	X*	X*	X*
Subject baseline questionnaire	X				
Subject follow-up questionnaire		X*	X*	X*	X*
* Only variations since last study visit will be collected.					

6 STUDY PROCEDURES

6.1 Study Procedures

The study flow chart described above summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below.

This study requires all subjects to provide a sample of ORG at baseline and, in the US, at each follow-up visit. The samples will be collected by using an oral rinse and the subject will be instructed to do a mouth wash and gargle to collect cells from both the oral cavity and the oropharynx. The test will not allow to discriminate the origin site in the case of positivity.

The collection of such samples by the participant dentists is not considered interventional, as the test is not invasive. Dentists are among the healthcare providers that are responsible for identifying any potential health hazard occurring in the subject oral cavity; moreover, they are involved in the detection of the oral HPV infection and throat cancer. Dentist and odontologist sites have been previously approached used to recruit subjects for oral HPV testing purposes in healthy subjects[37,38].

The test to be used for the detection of the infection, and identifying the genotype of the HPV, will be SPF10, as it is considered highly sensitive and is commercially available. The different tests commercially available have a highly variable sensitivity for the detection of the HPV infection. For this reason, the same test will be used consistently for analysis in all countries. The test will allow collection and analysis of ORG sample. Additional details on the test are available at Section 12.1 ORG test.

The sealed envelopes including the subject questionnaires that are not electronically completed and the ORG samples will be collected through a courier service and taken to IQVIA (questionnaires) or the central lab offices (biologic specimens) for processing as corresponds.

In the US, the subject questionnaire will be completed online by the subjects, through a link. The link will be provided by the dentist and will require the subject changing credentials at first login in to ensure confidentiality. The subject questionnaires can be completed from any electronic device and must be finalized before the subject proceeds with the study procedures. The dentists will never have access to the responses on the subject questionnaire but will be acknowledged on its completion.

The HPV vaccination status information will be collected by the dentists in the study eCRF. The dentist will ask the subject the vaccine information required.

The variables provided by the dentist will be entered by the dentist or collaborator to the eCRF specially designed for the study. The eCRF will be accessible through the Internet and each dentist and collaborator will have a personal unique ID.

The eCRF will allow defining filters in collected variables in order to avoid mistakes, as well as logic checks and filters in an effort to minimize errors in data entry. The eCRF will also allow the study team to obtain statistics on subjects' recruitment. A separate eCRF will be completed for each subject.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in the eCRF. Data must be entered into the eCRF in English. Designated site personnel must complete the eCRF as soon as possible after subject recruitment.

A Help Desk will be provided for all study dentists and collaborators during the whole study period in the local language.

6.1.1 Administrative Procedures

6.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

Specifics about the study and the study population will be added to the consent form template.

The informed consent will adhere to Institutional Review Board (IRB)/Ethic Review Committee (ERC) requirements, applicable laws and regulations and Sponsor requirements.

6.1.2 Subject data

After obtaining the informed consent, each subject will be identified through an ID code. The dentist will have a subject log matching the ID code with the subject name. The subject log will be specific for each site, kept in the study folder and will not be shared with other study personnel outside the site. A unique subject ID code will be used in all the study documents for a particular subject, no personal identifiers will be used at any time.

During the baseline visit the dentist will provide the participant subject with a paper questionnaire and an envelope when no electronic collection will occur. These two paper documents will have the subject study ID code. The paper questionnaire must be returned once completed, before leaving the dentist office, and closed in the sealed envelope to ensure data privacy. Additionally, the dentist will call the subject approximately two weeks after the baseline/study visit to confirm the HPV vaccination status details by asking the subject on the phone.

All the envelopes containing the completed questionnaires will be kept in a locked cabinet until they are collected by a courier service.

The dentist or collaborator will be also responsible for completing the subject eCRF which will include the subject health data, including age and gender and information on the subject HPV vaccination details. Each eCRF will be identified by the same subject ID than the questionnaire and the ORG sample. The eCRF will include checks for the inclusion and exclusion criteria and will have limits on the number to be included based on the reported age and gender to ensure that each dentist only recruits the number of subjects required per gender and age groups. Age and gender will be set as mandatory, and no subject will be considered valid if age and gender are not provided.

6.1.3 Laboratory Assessments

The participating dentists will collect the ORG sample using the test kit provided along with the rest of the study material (copies of ICF, subject questionnaires, and envelopes).

After obtaining the ORG sample from the subject, the dentist will keep it as per the kit instructions and will send the kits in batches to a central laboratory which will analyze the samples received. All the tests to be performed for this study will be conducted under the guidance of the central laboratory, except in instances in which law prohibits export of subject samples. In such instances, another central laboratory will be designated and will be required to work in agreement of the same procedures.

The results from laboratory tests will be available in an electronic portal where all test orders can be entered in and reported out as well. Dentists will not have access to the subjects' results.

6.1.4. Discontinuation

Not applicable in the European countries and Japan, only the baseline visit will be conducted, no follow-up visits are planned.

In the US, all subjects are required to do all the follow-up visits every 6 months up to a maximum of 24 (+ 1) months of follow-up. To maximize subject retention throughout the study in the US, the dentist or collaborator will contact the subject 1 to 2 weeks before each follow-up visit to remind on the follow-up visit, and to schedule the appointment within the study visit window.

6.1.5 Visit Requirements

Visit requirements are outlined in Section 5 Subject Recruitment and Study Flow Chart

7 Safety and Product Quality Complaint Reporting and Related Procedures

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol.

7.1 Adverse Event and Product Quality Complaint Reporting

7.1.1 INVESTIGATOR RESPONSIBILITY:

If adverse events (AEs) or product quality complaints (PQCs) are identified following use of Gardasil®, or any other Merck product, then the AE* and/or PQC must be reported according to Table 1.

*For the purposes of this protocol, the term "AE" collectively refers to the following reportable events (refer to section 7.2 for definitions):

- Serious adverse events (SAEs), including death due to any cause
- Non-serious adverse reactions (NSARs)
- Special situations
- Study-specific Health Outcomes of Interest (HOIs) that meet criteria for SAE/NSAR or special situation

AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to Table 1.

The investigator must evaluate each SAE for causality and record causality on the report form for each SAE and NSAR reported.

Patient Reported Outcomes which have the potential to collect SAEs following the use of Merck product/s will be screened for SAEs, by the investigator or qualified healthcare provider (or designee) and reported according to Table 4.

If an investigator becomes aware of any SAE, regardless of causality, including death due to any cause, or NSAR within 2 days of the ORG sample collection, the event must be reported**.** The investigator must evaluate each SAE and NSAR for causality and record the causality assessment on the AE form. SAEs and NSARs are submitted using the timeframes and process in Table 1. **Additionally, any SAE brought to the attention of an investigator at any time after the above specified time period must be** reported if the SAE if felt to be causally **related to the protocol-specified procedure. All subjects**

with SAEs related to protocol-specified procedures must be followed up for outcome.

Table 4 AE and PQC Reporting Timeframes and Process for Investigators and Suppliers

AEs AND PQCs	**INVESTIGATOR TIMEFRAMES**	**SUPPLIER TIMEFRAMES**
	Investigator to Supplier [1], [2]	**Supplier to Merck [3]**
SAE regardless of causality (including study-specific HOIs that meet criteria for SAE) Serious Special Situation, regardless of causality	24 hours from receipt	2 BD/3 CD from time of receipt from investigator
NSAR (including study-specific HOIs that meet criteria for NSAR) Non-serious Special Situation, regardless of causality	10 CD from receipt	10 CD from time of receipt from investigator
PQC with or without an AE (SAE/NSAR/Special situation)	24 hours from receipt	24 hours from time of receipt from investigator
Spontaneously reported AEs/PQCs for Merck products-submit using above timeframes		
Follow-up to any AE/PQC-submit using above timeframes		
BD-Business Day; CD-Calendar Day		
If the investigator elects to submit AEs/PQCs for **non-Merck products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.		
[1] Investigator to Supplier: AEs and PQCs for Merck study product and *other* Merck products are submitted to Supplier via fax or secure email **[2]** Supplier enters AEs for Merck study product into study database (or equivalent repository) for tabulation in study report **[3] Supplier to Merck:** Supplier submits AEs and PQCs for Merck study product and *other* Merck products to Merck for reporting to worldwide regulatory agencies as appropriate		
Submitting AEs and PQCs to Local Designated Point of Contact (DPOC): All AEs and PQCs must be submitted to Local DPOC Mailbox in English using the AE/PQC reporting form. France: +33180464041 Germany: +498945611652 Italy: +390636380756 or +39063339327 Japan: +81362389063 Spain: +34913210616 United Kingdom: +01748828801 United States: 1-215-616-5677		

7.1.2 STUDY REPORT:

The final study report, and any planned interim analysis, will include aggregate listings of all AEs collected for Gardasil® and will be provided to regulatory agencies by the sponsor as required.

The Risk Management Subteam (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report or any interim report. The safety and conclusion sections of the final study report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts

7.1.3 PERIODIC SAFETY UPDATE REPORTS:

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

7.2 DEFINITIONS

7.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

7.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

7.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events

include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

7.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 7.2.3.

7.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect

7.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnoses, treatment or procedures. Examples of HOIs include syncope, disease progression, or hypoglycaemia collected as study endpoints. HOIs may meet the criteria of an SAE/SAR, NSAR or special situation, and if so, must be collected as such, in addition to being collected as an HOI. Specifically, collected HOI data must be assessed for the criteria described herein and reported accordingly.

7.2.7 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

7.2.8 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

7.2.9 Sponsor's product

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

7.2.10 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

7.3 SPONSOR RESPONSIBILITY FOR REPORTING ADVERSE EVENTS

All adverse events will be reported to regulatory agencies, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.4 AE/PQC Reconciliation

Reconciliation will be performed between the safety database and study data to ensure all reportable AEs and PQCs were reported and received. Starting from when the first patient is enrolled through the end of data collection, all AEs and PQCs will be reconciled on a periodic basis.

Section Break

8 Statistical Analysis Plan

8.1 Statistical Methods

The statistical analysis will be conducted with SAS® statistical software or R. A detailed statistical analysis plan (SAP) will be prepared and accepted before the data analysis initiation.

All analyses will be performed at country and global level, if results are comparable between countries.

Since no hypotheses will be tested, study primary objectives will be addressed using descriptive statistics only. Given the real-world nature of the data, the use of multiple imputation methods for missing data would introduce bias as missing data cannot be considered completely at random (MCAR) or at random (MAR). Variables will not be imputed.

Continuous variables will be described with number of subjects with valid/missing observations, mean and its 95% confidence interval (CI), standard deviation (SD), median, 25 and 75 percentiles (P25 and P75, respectively), minimum and maximum. For non-normally distributed continuous variables geometric mean and its 95% CI will be reported too. Categorical variables will be described by frequencies and related percentages and its 95% CI per class level.

To assess a potential selection bias on subjects fulfilling the inclusion and exclusion criteria but not willing to participate, these subjects will be compared in terms of age and gender with those from subjects included in the study. If differences are obtained, statistical methods to adjust for age and gender will be discussed and described in the SAP.

In order to assess the potential bias, in the US, associated to the loss of follow-up and other discontinuation reasons, the study discontinuation rate will be compared according to the presence of oral HPV infection at baseline. If differences are not obtained the analysis of measures assessed in follow-up visits (incidence, persistence and clearance) will be analyzed taking into account only those subjects with available information in the corresponding follow-up visit. Otherwise, if differences are obtained statistical methods to adjust for loss of follow-up rates will be discussed and described in the SAP.

8.1.1 Primary Objective: Describe the Natural History of the Oral HPV Infection Based on Prevalence

In order to calculate the prevalence of HPV infections in the oral cavity and oropharynx, the number of subjects with HPV infection at baseline will be divided by the total number of subjects included by participant dentists. The prevalence of HPV infection will be calculated including all HPV genotypes and by HPV genotype (including genotypes with a higher prevalence).

The HPV infection will be assessed by the detection of HPV DNA in the ORG sample collected at the baseline visit.

8.1.2 Primary Objective: Describe the Natural History of the Oral HPV Infection based on Incidence, Persistence and Clearance in the US

8.1.2.1 Incidence

In order to calculate the incidence of HPV infections in the oral cavity and oropharynx, the number of subjects with HPV infection newly diagnosed during the follow-up period will be divided by the total number of subjects included by participant dentists without oral HPV infection at baseline. The incidence of HPV infection will be reported including all HPV genotypes and by HPV genotype (including genotypes with a higher incidence). To calculate the incidence for each HPV genotype, only those subjects without HPV infection of the corresponding genotype at baseline will be included.

The HPV infection will be assessed by the detection of HPV DNA in the ORG sample collected at the baseline visit and in each follow-up visit.

8.1.2.2 Persistence

The persistence of HPV infection will be reported at 6, 12, 18, and 24 months using the prospective data collected, incident and prevalent cases will be presented separately. In each time point, the persistence will be calculated dividing the number of subjects remaining positive for HPV by the total number of subjects with positive HPV in the previous visit. In addition, time to lack of detection of the HPV genotype identified in prior visits (no persistence) will be described using Kaplan-Meier curves. Time to lack of detection will be reported stratifying by prevalent (HPV + at baseline) and incident cases (new HPV + during the follow-up, negative at baseline) cases. The persistence will be assessed considering the detection of the same HPV genotype at 6, 12, 18, and 24 months apart in ORG samples through DNA testing.

Also, persistence by behavioral risk factors (tobacco/alcohol use) will be analyzed to better understand interaction.

8.1.2.3 Clearance

Clearance of HPV infection will be reported at 6, 12, 18, and 24 months using the prospective data collected, incident and prevalent cases will be presented separately. In each time point, the clearance will be calculated dividing the number of subjects with negative HPV (including all genotypes) by the total number of subjects with positive HPV in the previous visit. In addition, time to clearance will be described using Kaplan-Meier curves.

Clearance will be assessed considering clearance of all HPV genotypes at 6, 12, 18, and 24 months apart in ORG samples through DNA testing.

Due to limited sample size expected for clearance, the analysis by vaccination status has not been considered.

8.1.3 Secondary Objective: Describe Oral HPV Risk Factors, including Demographic and Sexual Behavioral Data

Demographic, clinical and sexual behavior data collected for the study will be compared according to the presence of oral HPV infection at baseline. Chi square test will be used for the comparison of categorical variables, and the Student t test for the comparison of continuous variables. A multivariate regression model (logistic regression model or poison regression model) will be used to assess risk factors associated to HPV infection (prevalence and incidence).

Variables with statistical significance in univariate analysis will be included in the multivariate model. The analysis of oral HPV risk factors will be performed with the overall sample, not at country level.

8.2 Bias

8.2.1 Methods to Minimize Bias

The distribution of the participating dentists between private and public clinics will be as close as possible to the characteristics of the dentist population in each country. The authors are aware that in some countries, i.e. Italy or Spain, where only private clinics may participate, the study sample may be slightly biased towards a higher economical level than the general population, this is reported as a study limitation.

To minimize selection bias, the participating dentists will be asked to invite to all subjects that meet the inclusion and exclusion criteria that they see consecutively in their clinic until they have recruited 5 subjects in a particular day. They will recruit subjects during 14 consecutive working days; this period of 14 working days may be extended up to a maximum of 40 working days or until they recruit 68 (or 69) subjects, whichever occurs first. The distribution of participant subjects by age and gender will be as detailed in section 3.3 Study Population.

8.2.2 Limitations

The main study limitation is the complexity to reach a sample of participating subjects who are representative of the general population. Dentists are considered to be the healthcare providers caring for the oral region health who see the highest number of general population with no major health issues in the oropharyngeal region. Additionally, the dentists have previously been involved in epidemiological studies aiming to estimate prevalence through analyzing ORG samples to assess the HPV infection and genotyping[39,40].

The involvement of private dentists to recruit the study subjects may introduce a bias towards subjects with higher economical level, due to the lack or limited public dental care in some of the participant countries, especially in Italy, Spain and the US.

The sites to participate will be those selected after completing the feasibility study. Some questions in the feasibility will be limiting for participation, such as certain characteristics of facilities (e.g. having a freezer to store the ORG samples) or the number of potential subjects to include in the study. For all the sites willing to participate and without any limitation on the feasibility, the study team will select those to be invited to participate based on the postal code provided. The postal code is a good indicator of the socioeconomic level of the population. When selecting the sites to participate, the study team will ensure they are spread across the country, include urban and rural sites and of different economic levels to be able to collect a representative sample of subjects. Given that the subjects will be recruited randomly, as they attend to the dentist visit, it is expected that they are representative of the socioeconomic level where the clinic is based. In addition to site selection, the postal code will be also used in order to assess the representativity of sites selected based on the socioeconomic level.

One approach for the US might be to compare prevalence (from this dental clinic study) with NHANES. It will also be important to compare other characteristics (demographic factors, SES, etc.) between dental clinic participants with the general US population (NHANES). If there is a

difference in prevalence (dental clinic study vs. NHANES), it would be interesting to see if a standardization approach (inverse probability weighting) using appropriate risk factors can correct the imbalance. One approach might be to try correcting using a large set of risk factors (measured in both our current study and NHANES) and a minimal set of risk factors (e.g., only demographics).

Also, the study might incur on subject selection bias, based on the sexual risk behavior or in the HPV vaccination status. The dentists will be asked to complete a log which will also collect gender and age of those not accepting to participate. The characteristics of the subjects not willing to participate will be described in the study report.

There is a risk of subjects not coming back to the dentist for the follow-up visits in the US, even if their frequency being in line with the recommendations of the health authorities. To decrease the number of subjects lost during the follow-up period, the study Sponsor may give stipends to subjects in the US for each visit performed. The stipends for the patients will be sufficient to the time they lose due to the study procedures .

Finally, the authors are aware that collecting the vaccination status will be challenging. In general, it is difficult to recall vaccination date and which vaccine was administered, in some cases subjects might not remember if they have been vaccinated for HPV either. For this reason, subjects will be asked on their vaccination status during the baseline but also the dentist or collaborators will call back to the subjects to confirm the information they have provided during the baseline in the questionnaire and provide any additional data, if available (i.e. vaccination dates or commercial name for the vaccine used). Still some subjects may not finally provide their vaccination status or vaccination details.

8.3 Sample Size and Power Calculations

The study sample has been calculated at country level in order to assess the study objectives defined for each region (European countries (France, UK, Germany, Spain and Italy), Japan and the US).

In European countries, the sample size has been calculated to estimate the prevalence of HR oral HPV infection (all and HR genotypes) by gender at country level. There is a high variability in prevalence rates in European studies. Data reported in a recent meta-analysis conducted to provide age-, sex-, and type-specific global and regional estimates of the prevalence of oral mucosal alpha-type HPV infection in healthy individuals has been used. Results from the meta-analysis has been used for sample size calculation due to the highest level of evidence provided by type of study. The meta-analysis allows to combine data derived from several studies ensuring the use of all evidence available applying the corresponding weights.

In Europe, the overall oral HPV prevalence (all genotypes) has been estimated in 6.5% (95% CI: 3.4% - 10.5%), and the HR oral HPV prevalence has been estimated in 3.6% (95% CI: 0.6% - 8.3%). HPV prevalence is also influenced by the sensitivity and the specificity of the HPV test used. Due to the lack of availability of standardized information about the sensitivity and specificity of HPV tests used in all studies, a conservative approach for sample size calculation has been used in order to ensure to have the sample size required. For each prevalence (all genotypes and HR genotypes) two scenarios for sample size calculation have been considered, the estimated prevalence (6.5% and 3.6%, respectively), as well as the upper limit of the 95% CI (10.5% and 8.3%, respectively)[29].

Several absolute precision levels and a significance level of 0.05 has been used to calculate the number of males and females to be included in the study using the following formula:

$$n = Z^2\alpha/2 \cdot (p \cdot (1\text{-}p) / MOE^2)$$

Where Zα/2 is the critical value of the Normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), MOE is the margin of error, and p is the estimated prevalence of oral HPV infection.

The following table describes the sample size calculation with several scenarios. A **sample of 1,164 subjects at country level** (582 males and 582 females) are required to reach an absolute precision level of 2.2, 2.6, 1.6, and 2.3 for a prevalence of 6.5%, 10.5%, 3.6% and 8.3%, respectively. A **total sample of 5,820 subjects from Europe** will be required.

Table 5 Sample size calculation by gender per all or HR HPV considering different scenarios for prevalence and absolute precision for each European country

	All HPV genotypes				**HR HPV genotypes**			
	Prevalence = 6.5%		**Prevalence = 10.5%**		**Prevalence = 3.6%**		**Prevalence = 8.3%**	
Absolute precision level (%)	**n by gender**	**Overall n**	**n by gender**	**Overall n**	**n by gender**	**Overall n**	**n by gender**	**Overall n**
1.4	717	1,434	1,568	3,137	717	1,434	1,568	3,137
1.5	624	1,248	1,367	2,735	624	1,248	1,367	2,735
1.6	960	1,920	1,483	2,966	**548**	**1,097**	1,202	2,404
1.8	759	1,518	1,172	2,344	434	867	951	2,006
2.0	615	1,230	950	1,900	352	703	769	1,539
2.1	615	1,230	862	1,724	319	638	698	1,396
2.2	**508**	**1,016**	786	1,572	291	581	637	1,274
2.3	465	930	719	1,438	266	533	**582**	**1,164**
2.4	427	854	660	1,320	244	488	535	1,069
2.6	364	728	**563**	**1,126**	208	417	456	912
2.8	314	628	485	970	180	360	393	785

In the US, the sample size has been calculated to estimate prevalence, incidence and persistence of HR oral HPV infection by gender.

In terms of prevalence, the most recent study performed using adults from NHANES (National Health and Nutrition Examination Survey) from 2011 to 2014, showed a prevalence of all HPV infection genotypes of 11.5% (95% CI, 9.8%−13.1%) in males and 3.2% (95% CI, 2.7%−3.8%) in females, and for HR HPV infection genotypes 7.3% (95% CI: 6.0%-8.6%) in males and 1.4% (95% CI: 1.0%-1.8%) in females, respectively[9]. As described in the sample size for European countries, two scenarios have been considered for each gender, the estimated prevalence, as well as the upper limit of the 95% CI.

Several absolute precision levels and a significance level of 0.05 has been used to calculate the number of males and females to be included in the study using the same formula described above for Europe. The following table describes the sample size calculation with several scenarios. Using the conservative approach, **a total sample of 2,968 subjects (1,419 males and 1,549 females)** is required to estimate the prevalence of 8.6% and 13.1% in males with an absolute precision level of 1.5% and 1.8%, respectively; and the prevalence of 1.8% and 3.8% in females with an absolute precision level of 0.7% and 1.0%, respectively. A 5% of invalid cases have been considered for sample size calculation.

Table 6 Sample size calculation by gender per all or HR HPV considering different scenarios for prevalence and absolute precision for the US

	All HVP genotypes				HR HPV genotypes			
	Males		Females		Males		Females	
	Prevalence = 11.5%	Prevalence = 13.1%	Prevalence = 3.2%	Prevalence = 3.8%	Prevalence = 7.3%	Prevalence = 8.6%	Prevalence = 1.4%	Prevalence = 1.8%
Absolute precision level (%)	n by gender	n by gender	n by gender	n by gender	n by gender	n by gender	n by gender	n by gender
0.6							**1,549**	1,983
0.7							1,139	**1,458**
0.8			1,955	2,305			873	1,116
0.9			**1,545**	1,822			689	883
1.0			1,252	**1,477**			559	716
1.2			870	1,026	1,898	2,203	388	497
1.3			742	875	1,618	1,878	331	423
1.4			640	755	**1,396**	1,620	285	365
1.5			557	657	1,216	**1,412**		
1.6	1,606	1,796	490	578	1,068	1,241		
1.8	**1,270**	**1,419**			845	981		
1.9	1,140	1,275			759	881		
2.0	1,028	1,150			684	795		
2.2	851	952			566	657		
2.3	778	871			518	601		
2.4	715	800						
2.5	659	737						
2.6	609	681						

The incidence of oral HPV will be analyzed in subjects without oral HPV infection at baseline and reported at overall level and by gender (not planned by age groups). HIM study has estimated the 12-months incidence of any genotype oral HPV infection in 4.4% (95% CI, 3.5%−5.6%); and HR oral HPV infection in 1.7% (95%CI: 1.2%-2.5%)[20]. However, there is a lack of information about the estimated incidence of HR oral HPV infection in women. It is expected that the incidence in females will be lower than in males, but with lower differences between both genders that for the prevalence. Taking into account a conservative approach (higher incidence rate), 1/2 and 1/3 of the incidence reported by males have been used for females providing different scenarios for calculations.

In males, the sample size has been calculated taking into account the estimated incidence and the 95% upper limit CI. For all HPV genotypes, the estimated sample of 1,419 males and 1,549 females in the US, followed during period of 2 years (corresponding to an overall sample of 2,564 males-years and 3,015 females-years) will allow to estimate 12-months incidence with an absolute precision level of 0.9-1.0% in males and 0.5% to 0.7% of absolute precision level in females (depending on the incidence estimate used). For HR HPV genotypes, the estimated sample of 1,419 males and 1,549 females in the US, followed during period of 2 years will allow to estimate 12-months incidence with an absolute precision level of 0.6% to 0.7% in males and 0.3% to 0.5% of absolute precision level in females (depending on the incidence estimate used). All calculations have been performed taking into account a significance level of 0.05 and taking into account a loss of follow-up of 15% of subjects during the two years follow-up period.

Table 7 Sample size calculation by gender per all or HR HPV considering different scenarios for incidence and absolute precision for the US

All HPV genotypes						
Absolute precision level (%)	**Males**		**Females**			
	Incidence = 4.4%	**Incidence = 5.6%**	**Incidence = 2.2% (1/2 of 4.4%)**	**Incidence = 1.5% (1/3 of 4.4%)**	**Incidence = 2.8% (1/2 of 5.6%)**	**Incidence = 1.9% (1/3 of 5.6%)**
0,4				4,157		
0,5			3,875	**2,664**		3,359
0,6			**2,695**	1,852	3,406	**2,335**
0,7			1,982	1,362	**2,505**	1,718
0.8	2,963	3,720	1,518	1,043	1,919	1,316
0.9	**2,343**	2,942	1,200	825	1,517	1,039
1.0	1,899	**2,385**	973	668	1,229	843
1.1	1,570	1,972	804			
1.2	1,320	1,658	676			
1.3	1,124	1,413				

HR genotypes						
Absolute precision level (%)	**Males**		**Females**			
	Incidence = 1.7%	**Incidence = 2.5%**	**Incidence = 0.85% (1/2 of 1.7%)**	**Incidence = 0.57% (1/3 of 1.7%)**	**Incidence = 1.25% (1/2 of 2.5%)**	**Incidence = 0.83% (1/3 of 2.5%)**
0.3			4,215	**2,838**		4,117
0.4			**2,376**	1,599	3,475	**2,320**
0.5	3,012		1,522	1,024	**2,228**	1,486
0.6	**2,094**	3,051	1,057	712	1,548	1,033
0.7	1,540	**2,244**			1,138	760
0.8	1,180	1,720				
0.9	933	1,359				

Persistence will be only assessed in HPV+ subjects, including prevalent and incident cases. For sample size calculation the measure of persistence at 6 months is considered. This will allow to include incident cases (newly diagnosed) until month 18 to ensure a 6 months follow-up period to assess persistence. Based on the estimated prevalence and incidence of all HPV genotypes (estimated prevalence, not 95% CI) in the US it is expected to identify 125 prevalent cases at baseline, 35 incident cases at 6 months, 35 incident cases at 12 months, and 34 incident cases at 18 months; obtaining a total estimated sample for persistence at 12 months of 229 subjects.

HIM study estimated a median time to clearance of 6.3 months for HR oral HPV infections. Therefore, the percentage of HR oral HPV infections persistent at 6 months is estimated in 50%. The estimated sample of 229 subjects to be included in persistence analysis will allow to estimate the persistence rate of 50% with an absolute prevision level of 7.3%, using a confidence level of 95% and taking into account a 20% of loss of follow-up.

Like in Europe, in Asian countries, the sample size has been calculated in order to estimate the prevalence of all genotypes and HR oral HPV infection. Studies performed in general population estimate the prevalence of HR oral HPV infection (95% CI) is 0.6% (95% CI:0.47%-0.93%)[11] and 2.5% (95% CI:1.8%-3.5%)[12] for all genotypes; and between 0.6% (95% CI:0.4%-1.0%)[11] and 0.8% (95% CI:0.4%-1.4%)[12] for HR HPV infection. Differences by gender have not been reported. As described in the sample size for European countries, two scenarios have been considered, the estimated prevalence, as well as the upper limit of the 95% CI. In Japan, the prevalence has been estimated in 0.6%.[13]

Several absolute precision levels and a significance level of 0.05 has been used to calculate the number of males and females to be included in the study using the same formula described above for Europe. The following table describes the sample size calculation with several scenarios. For all HPV genotypes prevalence, a **total sample of 1,168 subjects** is required to estimate the prevalence of 0.67%, 2.5%, and 3.5% with a precision level of 0.7%, 1.3% and 1.6%. For HR HPV genotypes prevalence, the same sample will allow to estimate the prevalence of 0.8% and 1.4% with a precision level of 0.8% and 1.0%, respectively.

Table 8 Sample size calculation by gender per all or HR HPV considering different scenarios for prevalence and absolute precision for Japan

	All HPV genotypes						HR HPV genotypes			
	Prevalence = 0.67%		Prevalence = 2.5%		Prevalence = 3.5%		Prevalence = 0.8%		Prevalence = 1.4%	
Absolute precision level (%)	n by gender	Overall n	n by gender	Overall n	n by gender	Overal l n	n by gender	Overall n	n by gender	Overall n
0.4	1,680	3,360					2,003	4,006	3,479	6,958
0.5	1,076	2,152					1,283	2,566	2,229	4,459
0.6	748	1,496					892	1,783	1,548	3,097
0.7	**550**	**1,100**					656	1,312	1,139	2,278
0.8							**502**	**1,004**	873	1,745
0.9									689	1,379
1.0			986	1,972					**559**	**1,118**
1.1			815	1,630	1128	2,256			462	924
1.2			685	1,370	949	1,898				
1.3			**584**	**1,168**	809	1,618				
1.4			503	1,006	697	1,394				
1.5					607	1,214				
1.6					**534**	**1,068**				

HPV genotype will be only reported in subjects with oral HPV infection. Based on the study sample and the estimated prevalence in participant countries, it is expected to identify 48 subjects with HR oral HPV infection in each EU country, 131 subjects in the USA, and 8 in Japan (considering the estimated prevalence, not the upper limit of the 95% CI), obtaining a total sample of 379 subjects with oral HPV infection.

At overall level, a total sample of 9,956 subjects, 2,968 subjects from the US, 1,164 subjects from each European country, and 1,168 subjects from Japan.

Table 9 Summary of sample size requirements by gender per each country

Countries	Males	Females	Total subjects
France	582	582	1,164
Germany	582	582	1,164
Italy	582	582	1,164
Spain	582	582	1,164

Countries	Males	Females	Total subjects
UK	582	582	1,164
Japan	584	584	1,168
US	1,419	1,549	2,968
Total	4,913	5,043	***9,956***

9 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Confidentiality

9.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

9.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative) or Institutional Review Board/Independent Ethics Committee (IRB/IEC), may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

9.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

9.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

9.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

9.4 Quality Management System

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

9.5 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

For an outsourced study the institutional policies of the supplier should be followed for development of data management plans. However, the supplier should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

10 Publications

The Risk Management Subteam (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report or any interim report. The safety and conclusion sections of the final study report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

Upon study completion and finalization of the study report, the results of this non-interventional study will be submitted for publication. Publications will follow the International Committee of Medical Journal Editors (ICMJE) guidelines. Data will be published for each country separately and combined publications will also be considered for selected outcomes (TBD).

The study results may not be published or disseminated without the prior permission of the study sponsor as per contract executed with the investigator.

11 References

[1] Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. Rev Med Virol. 2015 Mar; 25(Suppl 1): 2–23.

[2] Tam S, Fu S, Xu L, Krause KJ, Lairson DR, Miao H, et al. The epidemiology of oral human papillomavirus infection in healthy populations: A systematic review and meta-analysis. Oral Oncol. 2018;82:91-99.

[3] Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA. 2012;307(7):693-703.

[4] Chung CH, Bagheri A, D'Souza G. Epidemiology of oral human papillomavirus infection. Oral Oncol. 2014;50(5):364-9.

[5] Pickard RK, Xiao W, Broutian TR, He X, Gillison ML. The prevalence and incidence of oral human papillomavirus infection among young men and women, aged 18-30 years. Sex Transm Dis. 2012;39(7):559-66.

[6] Meyer MF, Huebbers CU, Siefer OG, Vent J, Engbert I, Eslick GD, et al. Prevalence and risk factors for oral human papillomavirus infection in 129 women screened for cervical HPV infection. Oral Oncol. 2014;50(1):27-31.

[7] Knight GL, Needham L, Ward D, Roberts S. Pilot study investigating the prevalence of oral Human Papilloma Viral (HPV) infection in young adults. Public Health. 2016r;132:105-7.

[8] Lupato V, Holzinger D, Höfler D, Menegaldo A, Giorgi Rossi P, Del Mistro A, et al. Prevalence and Determinants of Oral Human Papillomavirus Infection in 500 Young Adults from Italy. PLoS One. 2017;12(1):e0170091.

[9] Sonawane K, Suk R, Chiao EY, Chhatwal J, Qiu P, Wilkin T, et al. Oral Human Papillomavirus Infection: Differences in Prevalence Between Sexes and Concordance With Genital Human Papillomavirus Infection, NHANES 2011 to 2014. Ann Intern Med. 2017;167(10):714-724.

[10] Mena M, Taberna M, Monfil L, Arbyn M, de Sanjosé S, Bosch FX, et al. Might oral Human Papillomavirus (HPV) Infection in Healthy Individuals Explain Differences in HPV-Attributable Fractions in Oropharyngeal Cancer? A systematic review and meta-analysis. The Journal of Infectious Diseases 2018 (online publication)

[15] D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. PLoS One. 2014 Jan 24;9(1):e86023.

[16] Hearnden V, Murdoch C, D'Apice K, Duthie S, Hayward NJ, Powers HJ. Oral human papillomavirus infection in England and associated risk factors: a case-control study. BMJ Open. 2018;8(8):e022497.

[17] Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens--Part B: biological agents. Lancet Oncol. 2009; 10(4): 321-322.

[18] Steinau M, Saraiya M, Goodman MT, Peters ES, Watson M, Cleveland JL, et al; HPV Typing of Cancers Workgroup. Human papillomavirus prevalence in oropharyngeal cancer before vaccine introduction, United States. Emerg Infect Dis. 2014;20(5):822-8.

[19] Taylor S, Bunge E, Bakker M, Castellsagué X. The incidence, clearance and persistence of non-cervical human papillomavirus infections: a systematic review of the literature. BMC Infect Dis. 2016 Jun 14;16:293. doi: 10.1186/s12879-016-1633-9. Review.

[20] Kreimer AR, Pierce Campbell CM, Lin HY, Fulp W, Papenfuss MR, Abrahamsenet MR et al. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. Lancet. 2013;382(9895):877-87.

[21] Beachler DC, Sugar EA, Margolick JB, Weber KM, Strickler HD, Wiley DJ, et al. Risk factors for acquisition and clearance of oral human papillomavirus infection among HIV-infected and HIV-uninfected adults. Am J Epidemiol. 2015;181(1):40-53.

[22] Sanders AE, Slade GD, Patton LL. National prevalence of oral HPV infection and related risk factors in the U.S. adult population. Oral Dis. 2012;18(5):430-41.

[23] Golusinski P. Risk Factors for Oral Infection with Human Papillomavirus. Recent Results Cancer Res. 2017;206:73-85.

[24] Juckett G. Human Papillomavirus: Clinical Manifestations and Prevention, Am Fam Phys. 2010;82(10).

[25] Sheikh S, Biundo E, Courcier S, Damm O, Launay O, Maes E, et al. A report on the status of vaccination in Europe. Vaccine. 2018 Aug 9;36(33):4979-4992.

[26] National Center for Immunization and Respiratory Diseases. Human papillomavirus (HPV) vaccination coverage among adolescents 13-17 years by State, HHS Region, and the United States, National Immunization Survey-Teen (NIS-Teen), 2008 through 2017. Available at: https://www.cdc.gov/vaccines/imz-managers/coverage/teenvaxview/data-reports/hpv/trend/index.html Accessed: 25 April 2019.

[27] Paz-Zulueta M, Álvarez-Paredes L, Rodríguez Díaz JC, Parás-Bravo P, Andrada Becerra ME, Rodríguez Ingelmo JM, et el. Prevalence of high-risk HPV genotypes, categorised by their quadrivalent and nine-valent HPV vaccination coverage, and the genotype association with high-grade lesions. BMC Cancer. 2018 Jan 30;18(1):112.

[28] Donà MG, Pichi B, Rollo F, Benevolo M, Latini A, Laquintana V, et al. Human papillomavirus detection in matched oral rinses, oropharyngeal and oral brushings of cancer-free high-risk individuals. Oral Oncol. 2019 Apr;91:1-6.

[29] Mehanna H, Bryant TS, Babrah J, Louie K, Bryant JL, Spruce RJ, et al. Human papillomavirus (HPV) vaccine effectiveness and potential herd immunity for reducing oncogenic oropharyngeal HPV16 prevalence in the UK; a cross-sectional study. Clin Infect Dis. 2019; 69(8): 1296-302.

[30] Simonidesová S, Hamšíková E, Klozar J, Tachezy R. The prevalence of oral HPV infection in healthy populations: A systematic review with a focus on European populations. Epidemiol Mikrobiol Imunol. Winter 2018;67(4):175-183.

[31] Wood ZC, Bain CJ, Smith DD, Whiteman DC, Antonsson A.. Oral human papillomavirus infection incidence and clearance: a systematic review of the literature. J Gen Virol, 2017 Apr;98(4):519-526

[32] D'Souza G, Wentz A, Kluz N, Zhang Y, Sugar E, Youngfellow RM, ET AL. Sex Differences in Risk Factors and Natural History of Oral Human Papillomavirus Infection, J Infect Dis. 2016 Jun 15;213(12):1893-6

[33] WHO. Comprehensive cervical cancer control. A guide to essential practice - Second edition 2014. Available at: https://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/ Accessed: 14 February 2019.

[34] Mehanna H, Franklin N, Compton N, Robinson M, Powell N, Biswas-Baldwin N, et al. Geographic variation in human papillomavirus-related oropharyngeal cancer: Data from 4 multinational randomized trials. Head Neck. 2016;38 Suppl 1:E1863-9.

[35] Chaturvedi AK, Graubard BI, Broutian T, Pickard RKL, Tong ZY, Xiao W, et al. Effect of Prophylactic Human Papillomavirus (HPV) Vaccination on Oral HPV Infections Among Young Adults in the United States. J Clin Oncol. 2018;36(3):262-267.

[36] Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al; CVT Vaccine Group. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS One. 2013;8(7):e68329.

[37] Cab-Sánchez BG, Hernández-Solís SE, Rueda-Gordillo F, Conde-Ferráez L, Gómez-Carballo JG, González-Losa MDR. Epidemiología de la infección oral por VPH en sujetos jóvenes sanos. Rev Chilena Infectol. 2017 Dec;34(6):557-562.

[38] Hearnden V, Murdoch C, D'Apice K, Duthie S, Hayward NJ, Powers HJ. Oral human papillomavirus infection in England and associated risk factors: a case–control study. BMJ Open 2018;8:e022497.

[39] Conway DI, Robertson C, Gray H, Young L, McDaid LM, Winter AJ, et al. Human Papilloma Virus (HPV) Oral Prevalence in Scotland (HOPSCOTCH): A Feasibility Study in Dental Settings. PLoS One. 2016;11(11):e0165847.

[40] Rindal DB, Gilbert G, Carcelén C, Funkhouser E, Durand E, Uppgaard DA, et al; National Dental Practice-Based Research Network. Feasibility and acceptance of oral human papillomavirus detection in the dental office: Results from The National Dental Practice-Based Research Network. J Am Dent Assoc. 2019;150(2):130-139.e4.

12 Appendices

12.1 ORG test

The ORG samples will be collected using an alcohol containing solution. The participant subjects will be requested to gargle 15 mL of solution for 30 seconds. This alcohol containing solution will serve as a preservation solution which should preserve the biologic sample from degradation. The collected sample will be kept frozen in the dentist premises until a courier service can collect a batch of samples and send them to the central laboratory.

In the laboratory the samples will be centrifuged, and the residuum kept for testing. Depending on the tests to be performed the sample may need further manipulation.

For HPV DNA analysis, a PCR technique will be used to obtain the DNA for HPV genotyping identification purposes.

13 Attachments

Link to Adverse Event and Product Quality Compliant Report Form and Instructions

Adverse Event and Product Quality Compliant Report Form and Instructions

AdverseEvent_Prod
uctQualityComplaint

14 SIGNATURES

14.1 Sponsor's Representative

PRINTED NAME	**Edith Morais**
TITLE	**Director, Outcomes Research**
SIGNATURE	
DATE SIGNED	

14.2 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 6 – Safety and Product Quality Complaint Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

14.3 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 6 – Safety and Product Quality Complaint Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	**Nuria Lara**
TITLE	**IQVIA / Principal in charge**
SIGNATURE	
DATE SIGNED	