Protocol

An Open-label phase III study to investigate the safety, tolerability and immunogenicity of a nine-valent human papillomavirus (HPV) vaccine (Gardasil®9) in solid organ transplant recipients and HIV-infected patients

13 November 2018

***Version 4* – Amendement 1**

Investigational Medicinal Product (i.e. Study Vaccine):

GARDASIL®9

EudraCT NUMBER: 2017-004322-15

NTC number: NCT03525210

Sponsor: **University hospitals of Leuven (UZ Leuven)**

Principal investigator: Prof. Dr. Corinne Vandermeulen

Study coordinator: Lise Boey

Leuven University Vaccinology Center (LUVAC)
KU Leuven
Herestraat 49
3000 Leuven
☎ 016/34 20 20
email : corinne.vandermeulen@uzleuven.be
email : lise.boey@kuleuven.be

Sub-Investigators:

Prof. dr. I. Derdelinckx
Prof. dr. D. Kuypers
Prof. dr. J. Van Cleemput
Prof. dr. R. Vos

University hospitals of Leuven
Herestraat 49
3000 Leuven

Table of contents

List of tables

RATIONALE for Amendment 1

In the HIV group we anticipated a sample size of 140 patients which was deemed feasible since 471 HIV patients between 18 and 46 years of age were followed in the university hospitals of Leuven. However, at the start of study only a list of 366 eligible patients was available, of whom 69 have been enrolled in the study to date, 8 have discontinued treatment at the hospital, 105 patients will be approached in the near future and 198 had to be excluded during screening. The main reasons for exclusion were a history of condylomata (n = 56), a history of low grade vaginal, vulvar, cervix or anal neoplasia (n = 19), not deemed to be eligible by the treating physician, and no interest or no time. Based on the current response and eligibility rates, we estimate that in total about 70 patients can be included according to the current study protocol.

Based on this finding, literature on HPV vaccination in HIV patients was looked into again and a recalculation of the initial sample size was done based on the following findings:

- Prior to the start of the study, a sample size calculation was based on an expected seroconversion rate of 85%-91% for HPV type 18 (most stringent seroconversion rate) and allows to estimate the proportion of seroconverted patients with a margin of error (precision) of ±5.9% to ±4.7% (1). The expected seroconversion rates for types 6, 11, and 16 are higher (> 95%), and thus with a smaller margin of error (less then ±3.6%).
- The expected seroconversion rates that were used for the sample size calculation were retrieved from published data of patients with a CD4-count of 200-350 cells/mm². However, 92% of the patients that are currently included have a CD4-count of >350 cells/mm², which makes seroconversion rates in patients with more than 350 CD4+ cells/mm² more applicable (1). Published seroconversion rates in these patients are 95%-99% for HPV types 6, 11 and 16 and 90% for HPV-18.
- This sample size calculation does not take in to account that patients might be seropositive to certain HPV-types at baseline and that their data will be excluded for the analysis of the seroconversion outcome of the corresponding HPV-type. Seroprevalence to different HPV-types in previous studies on the safety and immunogenicity of the quadrivalent HPV-vaccine in HIV patients ranged from 13% to 45% for the different vaccine HPV-types (1–3).
- In order to maximize the number of eligible subjects, we amend the protocol to also **include patients with a history of abnormal PAP-smears without treatment or genital warts.** We believe that this allows us to reach a total sample size of at least 100 HIV-patients. Patients who are seropositive for a given HPV-type at baseline will

still be excluded for the analysis of seroconversion of that particular type but will still be useful for the analysis of the other HPV-types. Knowing that in HIV-patients the expected seroconversion rate of HPV-18 is relatively lower than the seroconversion rates of HPV types 6, 11 and 16, maximizing the number of eligible subjects for the analysis of this type is especially beneficial in order to obtain a reasonable margin of error. Enrolling patients with history of genital warts, who are most likely seropositive to HPV types 6 or 11, still allows us to increase the number of HPV-18 seronegative patients. In addition, clinical presentation of HPV infection does not necessarily implicate seropositivity to HPV.

- **With a total sample size of n=100, a majority of whom will have no history of HPV-lesions, we expect to be able to use the data of at least 80 patients for the analysis seroconversion of each HPV type under study. Seroconversion rates of 95-99% for HPV types 6, 11 and 16 can then be estimated with a margin of error of ±4.8% - 2.2%, and the anticipated seroconversion rate of 90% for HPV type 18 with a margin of error of ±6.6%.**

The amendment to the study protocol therefore includes an adaptation of the study protocol which consists of a reduction of the planned sample size (from 140 to 100), and a wider recruitment in order to fulfil the aims of the study.

ABBREVIATIONS AND DEFINITIONS

9vHPV	9-valent (6/11/16/18/31/33/45/52/58) human papillomavirus vaccine
AE	adverse event
ANSS	all type-specific naïve subjects with serology
cLIA	competitive Luminex® immunoassay
CRF	case report form
CSP	clinical study protocol
CSR	clinical study report
EDC	electronic data capture
EU	European Union
GMT	geometric mean titre
HIV	human immunodeficiency virus
HPV	human papillomavirus
ICF	informed consent form
IEC	independent ethics committee
IMP	investigational medicinal product
IRT	Interactive response technology
mAbs	monoclonal antibodies
mMU/mL	milli merck units per millilitre
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck&Co
PPI	per protocol immunogenicity
qHPV	quadrivalent human papillomavirus vaccine
SAE	serious adverse event
SOT	solid organ transplantation
VLP	virus-like particles

1. PROTOCOL SYNOPSIS

1.1. Title

An Open-label phase III study to investigate the immunogenicity and tolerability of a nine-valent human papillomavirus (HPV) vaccine (Gardasil®9) in solid organ transplant recipients and HIV-infected patients

1.2. Primary purpose of the study vaccine

Prevention of cervical, vulvar, vaginal and anal cancers and related precancerous lesions, external genital lesions, pap test abnormalities, and persistent infection caused by Human papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in transplant recipients and HIV-infected adults.

1.3. Rationale

Human papilloma virus (HPV) is the main cause of cervical malignancies (99%) and contributes to 90% of anal cancers, 40 % of vulvar, vaginal and penile cancers and causes in lower numbers oropharyngeal and mouth cancers (1). Up to 80% of women get infected with HPV during their lives, with the highest incidence 3 to 4 years after sexual onset (2). For men the risk of infection start shortly after sexual debut and remains high for the remainder of their life and about 30% of all HPV-related cancer occurs in men. In order to induce malignancies, persistent HPV infection is needed (3). In immunocompetent persons only 10% of the infections persist >6 months.

However, in immunocompromised patients, including transplant recipients and HIV-infected patients, chronic HPV-infection is more prevailing (4). Consequently, they have an increased risk for HPV-related complications. In healthy populations, HPV vaccination is very efficacious in preventing HPV infections. Studies showed a suboptimal immunogenicity of HPV vaccination in adult transplant patients but better immunogenicity in paediatric patients and HIV-infected patients with reasonable CD4-counts (>200 cells/mm² or CD4% ≥15) (5-13). However, in HIV and solid organ transplant patients, only a limited number of studies has been done with the bivalent and the quadrivalent vaccine, which comprises virus like particles (VLPs) of HPV types 16 and 18 and types 6, 11, 16 and 18 respectively.

In this study, the immunogenicity of the nine-valent HPV vaccine will be investigated in HIV and solid organ transplant patients, who will be recruited in the university hospitals of Leuven.

The nine-valent vaccine that will be used in this study comprises 5 additional VLPs of oncogenic HPV types 31, 33, 45, 52 and 58 compared to the quadrivalent vaccine and consequently has an additional preventive benefit, as it increases the coverage of all cervical cancers from 70% to 90% (14). In clinical trials in women and men (16 to 26 years of age) as well as in girls and boys (9 to 15 years of age), the 9-valent vaccine was well tolerated and prevented infection and disease due HPV types included in the

vaccine (15-17). The Gardasil®9 [1] was licensed in the US, Canada, Australia and Europe in respectively 2014 and 2015.

Gardasil®9 is currently approved for use in persons (boys and girls) as of nine years of age (Belgian SPC). Currently there are no data available for men or women above 26 years of age. Nevertheless, data are available on women 24 to 46 years of age for quadrivalent Gardasil®[2] vaccine from the FUTURE III trial. By the end of this clinical trial, data of the V503-004 study which enrolled women between 16 and 45 years of age might be available.

1.4. Summary of study design

This is a single-center, open-label study on safety, tolerability and immunogenicity of Gardasil®9 in 18 to 45 year-old HIV patients, in 18 to 55 year-old solid-organ transplant (SOT) patients.

This study will enrol 100 HIV patients with CD4+ count of >200cells/mm² and 170 SOT patients, all of whom have not yet received a prophylactic HPV vaccine. The 170 SOT patients will be equally divided over 3 different SOT patient groups, namely heart, lung and kidney transplant patients. Therefore the target is to include approximately 57 heart transplant patients, 57 lung transplant patients and 57 kidney transplant patients. Enrolment in a SOT subgroup will be stopped when 57 patients have been included unless recruitment cannot be achieved within one of the other SOT-patient population.

All enrolled subjects will receive a 3-dose regimen (Day 1, Month 2, and Month 6) of GARDASIL®9. Serum samples will be collected on Day 1 and Month 7 for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody determination. The time point for comparison of immune responses will be Month 7, or approximately 4 weeks after the administration of the third dose. The safety/tolerability profile of the vaccine will be evaluated in all subjects in the study. Safety information will be collected on Day 1 through 1 month following the third vaccination or for a total of approximately 7 months for each subject.

The immunogenicity and the safety data will be analyzed per group of patients. More specifically a separate analysis of HIV and SOT patients is planned, since it is expected that the immunosuppressive therapy of SOT patients might have a more profound effect on immunogenicity following vaccination.

This study will provide a comparison of immunogenicity of Gardasil ®9 in immunocompromised patients, with historical controls (15, 18). The number of subjects to be enrolled in the study was determined based on the primary immunogenicity objective.

[1] GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant) is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A

[2] GARDASIL [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A. GARDASIL is also known as SILGARD in some countries. SILGARD is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

1.5. Dosage/Dosage Form, Route, and Dose Regimen

Subjects will receive GARDASIL®9 (HPV 9-valent vaccine [recombinant, adsorbed]) administered as a 0.5-mL intramuscular injection on Day 1, Month 2 and Month 6. The vaccine formulation is summarized in Table 1. GARDASIL®9 is available as a suspension for injection. It appears as a clear liquid with white precipitate.

Table 1: Vaccine Formulation (0.5 mL Dose)

HPV 6 (mcg)	HPV 11 (mcg)	HPV 16 (mcg)	HPV 18 (mcg)	HPV 31 (mcg)	HPV 33 (mcg)	HPV 45 (mcg)	HPV 52 (mcg)	HPV 58 (mcg)	Total VLP (mcg)	AAHS† (mcg)
30	40	60	40	20	20	20	20	20	270	500
† AAHS, Merck Aluminum Adjuvant (amorphous aluminum hydroxyphosphate sulfate) HPV, human										

1.6. Study flow chart

Visit Windows (a) for SOT group	**Consent visit**	**2 months after Day 1, ±4 weeks**	**6 months after Day 1, -1 week / +4 weeks**	**3 to 7 weeks after Month 6**
Visit Windows (a) for HIV group	**Consent visit**	**2 months after Day 1, , -4 weeks / +2 weeks**	**6 months after Day 1, ±4 weeks**	**3 to 7 weeks after Month 6**
Procedures	**Visit 1 (Day 1/ Month 0)**	**Visit 2 (Month 2)**	**Visit 3 (Month 6)**	**Visit 4 (Month 7) (b)**

Obtain informed consent form	X			
Assign screening number	X			
Review inclusion/exclusion criteria (c)	X			
Collect medical history (past year)	X			
Collect demographics	X			
Collect weight/height	X			
Update medical history (new conditions not yet recorded as medical history or adverse events (AEs)		X	X	X
Review medications and non-study vaccines (d)	X	X	X	X
Pregnancy test (urine) (e)	X	X	X	X
Collect oral/tympanic temperature (f)	X	X	X	
Assign allocation number	X			
Provide diary card	X	X	X	
Review and collect vaccination diary data		X	X	X
Blood sample for anti-HPV antibody testing (including retention serum) (10 ml blood each time) (g)	X			X
Vaccination (Intramuscular, prefer deltoid muscle of non-dominant arm; do not give into buttocks)	X	X	X	
Provide vaccination diary	X			
Review vaccination diary (h)		X	X	X
Review AE's, clinical follow up for safety (i)	X	X	X	X

(a) To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days.

(b) Whenever possible, when a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation except for serum collection for HPV testing.

(c) A physical examination may be performed during Visit 1 if deemed necessary by the investigator to assess eligibility criteria.

(d) See Section 3.2.4. for details of documentation times and time period restrictions for medications and non-study vaccines. If other non-study vaccines are administered at any time during the study, they should not be administered in the same limb as the study vaccine and must be appropriately documented.

(e) The serum or urine pregnancy test will be performed per the manufacturer's instructions. A pregnancy test will be performed before administration of each dose of the study vaccine and at the final Month 7 visit on all female subjects. The pregnancy test must be performed prior to serum collection for HPV testing at Day 1.

(f) If the subject has a fever (defined as an oral temperature of ≥37.8°C) within the 24-hour period prior to receiving a study vaccination, the subject should not receive study vaccine, and the vaccination visit should be rescheduled until after the fever has resolved. Oral temperature will be measured prior to each vaccination

(g) Blood sample for anti-HPV measurements must be collected prior to the first study vaccination. Serum must be shipped as specified by MSD. The retention serum vial must remain at the study site until the MSD notifies the study site to ship the samples

(h) The investigator should instruct the subject to use the vaccination diary to document oral temperature in the evening after each study vaccination and daily, at the same time of day, for 4 days after each study vaccination. Additionally, injection-site and systemic adverse event(s) (AEs), concomitant

medications, and concomitant vaccinations are to be documented in the vaccination diary starting after each study vaccination for a total of 15 days, including the day of vaccination (Day 1 to Day 15).

(i) Observe subjects for at least 15 minutes after each vaccination for immediate untoward effects. Serious adverse events (SAEs), pregnancy events, and lactation events should be reported to MSD Belgium, within 24 hours. Adverse events and SAEs will be followed for 15 days and during the whole study, respectively, after the last dose (i.e., after the third dose for subjects completing the vaccination schedule or after the last received dose in the event of the subject withdrawing).

2. CORE PROTOCOL

2.1. Rationale

Human papilloma virus (HPV) is the main cause of cervical malignancies and contributes to 90% of anal cancers, 40 % of vulvar, vaginal and penile cancers and causes in lower amounts oropharyngeal and mouth cancers (1). Up to 80% of women get infected with HPV during their lives, with the highest incidence 3 to 4 years after sexual onset (2). For men the risk of infection start shortly after sexual debut and remains high for the remainder of their life and about 30% of all HPV-related cancer occurs in men. In order to induce malignancies, persistent HPV infection is needed (3). In immunocompetent persons only 10% of the infections persist >6 months.

However, in immunocompromised patients, including transplant recipients and HIV-infected patients, chronic HPV-infection is more prevailing (4). Consequently, they have an increased risk for HPV-related complications. In healthy populations, HPV vaccination is very efficacious in preventing HPV infections. Studies showed a suboptimal immunogenicity of HPV vaccination in adult transplant patients but better immunogenicity in paediatric patients and HIV-infected patients with reasonable CD4-counts (>200 cells/mm² or CD4% ≥15) (5-13). However, in HIV and solid organ transplant patients, research has only been done with the bivalent and the quadrivalent vaccine, which comprises virus like particles (VLPs) of HPV types 16 and 18 and types 6, 11, 16 and 18 respectively.

In this study, the immunogenicity of the nine-valent HPV vaccine will be investigated in HIV and solid organ transplant patients, who will be recruited in the university hospitals of Leuven. This tertiary hospital is large hospital located in the center of Belgium and is a reference center where patients from all over the country are treated. Approximately 415 heart, 590 lung and 700 kidney transplant patients are followed in the hospital, of whom approximately 160, 210 and 350 are between 18 and 55 years of age, respectively. About 900 HIV patients are equally followed in the university hospital of whom 470 are between 18 and 45 years old.

The nine-valent vaccine that will be used in this study comprises 5 additional VLPs of oncogenic HPV types 31, 33, 45, 52 and 58 compared to the quadrivalent vaccine and consequently has an additional preventive benefit, as it increases the coverage of all cervical cancers from 70% to 90% (14). In clinical trials in women and men (16 to 26 years of age) as well as in girls and boys (9 to 15 years of age), the 9-valent vaccine was well tolerated and prevented infection and disease due HPV types included in the vaccine (15-17). The Gardasil®9 was licensed in the US, Canada, Australia and Europe in respectively 2014 and 2015.**Gardasil®9 is currently approved for use in persons (boys and girls) as of nine**

years of age (Belgian SPC). Currently there are no data available for men or women above 26 years of age. Nevertheless, data are available on women 24 to 46 years of age for quadrivalent Gardasil® vaccine from the FUTURE III trial. By the end of this clinical trial, data of the V503-004 study which enrolled women between 16 and 45 years of age might be available

2.2 Objectives and hypothesis

2.2.1. Primary Objective Immunogenicity:

To determine the *immunogenicity* of Gardasil®9 with respect to HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 in adult HIV (age: 18-45 years) and transplant patients (age: 18-55 years).

Hypothesis: GARDASIL®9 induces in 18-45-year-old **HIV patients** (>200 CD4 T cells/mm²) seroconversion rates for HPV 6, 11 16, 18, 31, 33, 45, 52, and 58 at 4 weeks after Dose 3 that are similar to those induced in historical controls (healthy persons between 18 and 45 years of age. If the proposed control data are not available, immunogenicity will be compared to data from male and female healthy persons between 18 and 26 years of age and previous data from the immunogenicity of Gardasil® in HIV patients). The seroconversion rate for each of the HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be tested separately.

Hypothesis: GARDASIL®9 induces in 18-55-year-old **solid organ transplant patients** seroconversion rates for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks after Dose 3 that are similar to those induced in historical controls (healthy persons between 18 and 45 years of age. If the proposed control data are not available, immunogenicity will be compared to data from male and female healthy persons between 18 and 26 years of age). The seroconversion rate for each of the HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be tested separately.

(Seroconversion is defined as changing serostatus from seronegative at Day 1 to seropositive (antibody titer above seroconversion cut-off) by 4 weeks after Dose 3)

2.2.2. Secondary Objective(s):

SAFETY

To determine the *safety and tolerability* of Gardasil®9 with respect to HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 in adult HIV (age: 18-46 years) and solid organ transplant patients (age: 18-55 years).

Hypothesis: GARDASIL®9 is well tolerated 18-45-year-old **HIV patients** compared to healthy subjects as evaluated by the occurrence of local and systemic reactions following vaccination.

Hypothesis: GARDASIL®9 is well tolerated by 18-55-year-old **solid organ transplant patients** compared to healthy subjects as evaluated by the occurrence of local and systemic reactions following vaccination.

IMMUNOGENICITY

2.3. Subject inclusion criteria

To be included in the study and to receive the first study vaccination, subjects must meet all inclusion criteria. For items with an asterisk (*), if the subject does not meet these inclusion criteria, the Day 1 visit may be rescheduled to a time when these criteria can be met.

1. Independent Ethics Committee (IEC)-approved written informed consent form (ICF) must be obtained from the subject prior to any study-related procedure (including discontinuation of prohibited medication, if applicable) as required by local law.
2. Subject (man or woman) is between the age of 18 years and 0 days and 45 years and 365 days for HIV patients, between 18 years and 0 days and 55 years and 365 days for transplant patients at time of signing the ICF.
3. Subject is able to understand and adhere to the study procedures (e.g., is not planning to relocate far from the investigational centre during the study period); is able to read, understand, and complete the vaccination diary; is able to understand the risks involved with the study; and voluntarily agrees to participate in the study by giving written informed consent.
4. * Since the first day of their last menstrual period through Day 1, female subjects have not had sex with males or has had sex with males and used effective contraception with no failures (an example of a failure is a male condom that ruptures during sexual intercourse). Effective contraception is defined as a marketed, approved contraceptive product that the subject has used per the manufacturer's instructions with every act of sexual intercourse. The subject understands and agrees that during the Day 1 through Month 7 period, she should not have sexual intercourse with males without effective contraception. The use of the rhythm method alone, withdrawal alone, and emergency contraception, are not acceptable methods per the protocol. Subjects who have reached menopause, undergone hysterectomy, bilateral oophorectomy, or bilateral tubal ligation are eligible without the use of contraceptives. Postmenopausal status is defined as: (1) No menses for >1 year but <3 years and confirmed by follicle stimulating hormone (FSH) levels elevated into the postmenopausal range, or (2) no menses for at least 3 years.
5. * Subject has had no temperature ≥37.8°C within 24 hours prior to the first injection.
6. Patient considerations

- **HIV patients**: have CD4+ T cell count of >200 cells/mm² at the last control (less than 16 months ago).
- **SOT patients** received their organ transplantation ≥12 months prior to vaccination and has been stable in the past 6 months (i.e. no acute rejection or other immunological reactions).

7. Apart from having HIV or received a solid organ transplant, the subject is in stable condition (i.e. no graft-versus-host disease or other immunological reactions) and is judged to be in good physical health on the basis of medical history, physical examination (if deemed necessary), and laboratory testing
8. Subject agrees to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes.

2.4. Subject exclusion criteria

To be included and receive the first study vaccination, subjects should not have any exclusion criteria. For items with an asterisk (*), if the subject meets these exclusion criteria, the Day 1 visit may be rescheduled for a time when these criteria are not met.

1. Subject has a history of an abnormal Pap test or abnormal cervical biopsy results (showing cervical intraepithelial neoplasia or worse) or cervical disease (i.e., surgical treatment for cervical lesions).
2. **Patient medical history regarding HPV lesions:**
   a. **Exclusion criterion for HIV patients:** Subject has history of high grade Anal Intraepithelial Neoplasia, high grade Vulvar Intraepithelial Neoplasia or high grade Vaginal Intraepithelial Neoplasia.
      - history of anal or peri-anal condyloma is allowed

   b. **Exclusion criterion for SOT patients**: Subject has history genital warts, Anal Intraepithelial Neoplasia, Vulvar Intraepithelial Neoplasia or Vaginal Intraepithelial Neoplasia.
3. Subject has a history of known prior vaccination with an HPV vaccine, i.e., received a marketed HPV vaccine, or has participated in an HPV vaccine clinical study and has received either active agent or placebo.
4. Subject is pregnant (as determined by serum or urine pregnancy test).
5. Subject is, at the time of signing ICF, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence. Alcohol abusers are defined as those who drink despite recurrent social, interpersonal, and/or legal problems as a result of alcohol use.

6. Subject has a history of severe allergic reaction, including known allergy to any vaccine component, including aluminum, yeast, or BENZONASE® (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]) (e.g., swelling of the mouth and throat, difficulty breathing, hypotension or shock) that met the criteria for serious adverse experiences defined in this protocol.

7. **Patient's condition**
   a. **Exclusion criterion only for HIV patients:** Subject has had a splenectomy, or has been diagnosed as having a congenital immunodeficiency, lymphoma, leukaemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, or other autoimmune or immunosuppressive condition, or has a history of any disease, which, in the investigator's opinion, may confound the results of the study or pose an additional risk to the subject.
   b. **Exclusion criterion only for SOT patients**: Subject has had a splenectomy, or has been diagnosed as having a congenital or acquired immunodeficiency, HIV infection, lymphoma, leukaemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, or other autoimmune or immunosuppressive condition, or has a history of any disease, which, in the investigator's opinion, may confound the results of the study or pose an additional risk to the subject.

8. Patient's medication
   a. **Exclusion criterion only for HIV patients:** Subject is receiving or has received in the year prior to enrolment the following immunosuppressive therapies: radiation therapy, cyclophosphamide, azathioprine, methotrexate, any chemotherapy, cyclosporin, leflunomide (tumour necrosis factor-α antagonists, monoclonal antibody therapies (including rituximab [Rituxan]), intravenous gamma globulin, antilymphocyte sera, or other therapy known to interfere with the immune response. With regard to systemic corticosteroids, a subject will be excluded if she is currently receiving steroid therapy, has recently (defined as within 2 weeks of enrolment) received such therapy, or has received 2 or more courses of high dose corticosteroids (≥20mg/day of prednisone [or equivalent] orally or parenterally) lasting at least 1 week in duration in the year prior to enrolment. Subjects using inhaled, nasal, or topical corticosteroids are considered eligible for the study
   b. **Exclusion criterion only for SOT patients:** Subject is receiving or has received in the year prior to enrolment the following immunosuppressive therapies: radiation therapy, cyclophosphamide, methotrexate, any chemotherapy, leflunomide (tumour necrosis factor-α antagonists, monoclonal antibody therapies (including rituximab [Rituxan]) ,intravenous gamma globulin or antilymphocyte sera.

9. Subject has received any immune globulin or blood-derived product within the 3 months prior to the Day 1 vaccination, or plans to receive any such product during Day 1 through Month 7 of the study.

10. Subject has thrombocytopenia or other coagulation disorder that would contraindicate intramuscular injections.
11. * Subject has received inactivated vaccines within 14 days prior to the Day 1 vaccination or has received replicating (live) vaccines within 28 days prior to the Day 1 vaccination. The administration of the inactivated influenza vaccine is allowed 7 days prior to or after each study vaccine.
12. Subject is concurrently enrolled in a clinical study of investigational agent.
13. Subject has a history or current condition of which the investigator believes that it might interfere with the study vaccines.
14. Subject has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might confound the results of the study, or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate.
15. Subject is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial.

2.5. Study design and duration

2.5.1. Study design summary

This is a single-center, open-label study on immunogenicity and tolerability of Gardasil®9 in 18 to 45 year-old HIV patients, in 18 to 55 year-old solid-organ transplant (SOT) patients.

This study will enrol 100 HIV patients with CD4+ count of >200cells/mm² and 170 SOT patients, all of whom have not yet received a prophylactic HPV vaccine. The 170 SOT patients will be equally divided over 3 different SOT patient groups, namely heart, lung and kidney transplant patients. Therefore the target is to include approximately 57 heart transplant patients, 57 lung transplant patients and 57 kidney transplant patients. Enrolment in a SOT subgroup will be stopped when 57 patients have been included unless recruitment cannot be achieved within one patient population.

All enrolled subjects will receive a 3-dose regimen (Day 1, Month 2, and Month 6) of GARDASIL®9. Serum samples will be collected on Day 1 and Month 7 for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody determination. The time point for comparison of immune responses will be Month 7, or approximately 4 weeks after the administration of the third dose. The safety/tolerability profile of the vaccine will be evaluated in all subjects in the study. Safety information will be collected on Day 1 through 1 month following the third vaccination or for a total of approximately 7 months for each subject.

The immunogenicity and the safety data will be analyzed per group of patients. More specifically a separate analysis of HIV and SOT patients is planned, since it is expected that the immunosuppressive therapy of SOT patients might have a more profound effect on immunogenicity following vaccination.

This study will provide a comparison of immunogenicity of Gardasil ®9 in immunocompromised patients, with historical controls (15, 18).The number of subjects to be enrolled in the study was determined based on the primary immunogenicity objective.

2.5.2 Treatment plan

All enrolled 100 HIV patients and 170 SOT patients will receive GARDASIL®9 as a 3-dose regimen of 0.5-mL intramuscular injections administered on Day 1, Month 2, and Month 6. Study vaccine must be stored in a refrigerator that has a temperature between 2 °C and 8°C. If the refrigerator in which the study vaccine is stored deviates from the 2°C to 8°C range, study vaccinations should be suspended and MSD should be contacted immediately so that an investigation can be conducted.

2.6. List of immunogenicity measures

Serum will be collected for analysis of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 responses by competitive Luminex® immunoassay (cLIA). Serum will be analysed to support the primary objective. At Day 1, blood samples will be collected prior to the first study vaccination to identify subjects who have been exposed to study vaccine HPV types prior to enrolment. Serology results at Day 1 are not part of the inclusion/exclusion criteria; thus, no subject will be excluded from the study based on these results. After Day 1, serum specimens will be collected at the Month 7 study visit as specified in the Study Flow Chart (Section 1.6).

2.7 List of Safety Measurements

Each subject will receive a vaccination diary at the Day 1, Month 2, and Month 6 study vaccination visits. In the diary, the subject will be asked to record oral temperature in the evening after each study vaccination and daily, at the same time of the day, for 4 days after each vaccination, starting at the day of vaccination, for the purpose of identifying febrile events. In addition, beginning after each study vaccination and for a total of 15 days including the day of vaccination (Day 1 to Day 15), the subject will be asked to record injection-site and systemic adverse events (AEs), concomitant medications, and concomitant vaccinations on the vaccination diary. Serious adverse events (SAEs), pregnancy information, and lactation information will also be collected as described in Section 3.4. In addition, new medical conditions not present at baseline and not reported as an AE (i.e., incident medical conditions occurring outside of a Day 1 to Day 15 period post-vaccination and not considered SAEs) will be collected throughout the study. In case of pregnancy, the pregnancy and any serious adverse experiences in study subjects and their infants must be followed to outcome. In addition, if subjects receive study vaccine while breastfeeding during the Day 1 through Month 7 period, any serious adverse experiences in the study subjects and their infants must be followed to outcome.

2.8 Data monitoring committee

Since its market introduction in 2006, over 183 million doses of GARDASIL® have been distributed (as of April 2015). The safety profile is well characterized and continuously monitored by routine post-marketing surveillance activities. In June 2015, GARDASIL®9 (V503) was granted marketing authorization in Europe. Previous studies with Gardasil® in immunocompromised patients did not reveal any specific safety issues. Gardasil®9 is also an inactivated vaccine and not a live vaccine. Therefore the need for a Data Monitoring Committee was not deemed necessary in this context.

3.0. Protocol details

3.1. Study procedures

3.1.1. Identifying Study Subjects

Subject identification will be done in collaboration with the different clinical treating specialists (infectious disease specialists and transplant specialists) in order to include patients who comply with all in- and exclusion criteria. The patients will be informed about the possibility to participate in the current study by the treating specialist during a routine medical check- up. A dedicated person will then inform the patient about the objectives, obligations, possible benefits and risks of the study. The investigator will mention that the participation is voluntary and that withdrawal from the study or non-participation in the study will have no effect on the care to which the subject is otherwise entitled.

3.1.2. Informed Consent

Written informed consent will be obtained prior to any study procedure is started. The patient will be given sufficient time to consider participation in this clinical trial and will be given the opportunity (if necessary) to discuss his participation with his GP. 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 trial. 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 trial. 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. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

3.1.3. Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation, site personnel will add the allocation number to the Subject Identification Card.

3.1.4. Concomitant Medication(s)/Treatment(s)

See the exclusion criteria for specific restrictions for prior and concomitant medications at Day 1. Use of medicines and non-study vaccines will be reviewed at each visit and should be documented in the individual subject's Case Report Form (CRF) in the following manner:

- "Special Medications" (corticosteroids, immunosuppressives, immune globulins, and blood products) from 3 days prior to Day 1 through Month 7;

- "Other Medications" from 3 days prior to each study vaccination through 1 5 days (Day 1 to Day 15) after each study vaccination;
- "Non-Study Non-Replicating (Inactive) Vaccines" for 14 days prior to each study vaccination through 15 days (Day 1 to Day 15) after each study vaccination; and
- "Non-Study Replicating (Live) Vaccines" for 28 days prior to each study vaccination through 28 days (Day 1 to Day 28) after each study vaccination.

If possible, the subject should not receive special medications or non-study vaccines within the time periods given above. Subjects may receive allergen desensitization therapy and tuberculin skin testing while participating in the study.

3.1.5. Assignment of Allocation Number

All consented subjects will be given a unique allocation number that will be used to identify the subject for all procedures that occur prior to vaccine allocation. Each subject will be assigned only one allocation number, corresponding to the subject's condition (HIV vs SOT; (001) (002 -004)). Allocation numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original allocation number assigned at the initial screening visit. The allocation number also identifies the subject for all procedures occurring after screening.

3.1.7. Vaccination and Evaluation

All subjects will receive vaccination at the Day 1, Month 2 and Month 6 visit. Subject will be observed for 15 minutes after vaccination for any untoward adverse event.

3.1.8. Management of Pregnant Subjects

All female subjects will have a urine pregnancy test performed before administration of each dose of the study vaccine and at the final Month 7 visit per the manufacturer's instructions. Any subject with a positive pregnancy test at Day 1 will not be vaccinated and will not be allowed to participate in the study. For subjects who become pregnant after receiving one or two study vaccinations, study visits and vaccinations will be paused until resolution of the pregnancy (e.g. term, elective termination, spontaneous abortion). Study visits and study vaccination in pregnancy subjects will be handled as described in Table 2. Breastfeeding is not a contraindication to receiving study vaccinations. Pregnancy and breast-feeding in study subjects and infant serious adverse experiences (SAEs) must be reported as described in Section 3.4.

Table 2: Guidelines for Pregnant Subjects: Managing Study Visits and Study Vaccinations

Time When Pregnancy is Detected	Action
Day 1 (before first vaccination)	Do not vaccinate subject
Between Day 1 and Month 2 *(After study vaccine dose 1 and before study vaccine dose 2 was administered)*	- No scheduled visits until resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion). - The Month 2 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels. - The Month 6 study vaccination should be administered 4 months after the Month 2 study vaccination. - The Month 7 visit should be conducted 1 month after the Month 6 study vaccination.
Between Month 2 and Month 6 *(After study vaccine dose 2 and before study vaccine dose 3 was administered)*	- No scheduled visits until resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion). - The Month 6 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels. - The Month 7 visit should be conducted 1 month after the Month 6 study vaccination.
After Month 6 *(After study vaccine dose 3 was administered)*	- Continue with scheduled study visits during the pregnancy. - Safety follow-up will be conducted after resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion).

3.1.9. Dosage and Administration

Study vaccine will be administered at Day 1, Month 2, and Month 6. At each visit, subjects will receive GARDASIL®9 as a 0.5-mL intramuscular injection using a syringe. Injections should be administered at a 90° angle into the muscle tissue using a needle long enough to ensure intramuscular deposition of vaccine. The deltoid muscle of the non-dominant arm is the preferred site of vaccination. Study vaccines

should not be administered into the buttocks area. Injections should not be given within 2 cm of a tattoo, scar, or skin deformity. The subject should be afebrile (oral temperature <37.8ºC) for 24 hours prior to each vaccination. If the subject reports having been febrile within this 24-hour pre-vaccination period, no vaccination will be administered to the subject. The subject should be rescheduled to return for the vaccination visit once the fever has been resolved for at least 24 hours. If other non-study vaccinations are administered at any time during the study, they should not be administered in the same limb as the study vaccine and must be appropriately documented. The injection site for these non-study vaccines must also be documented.

3.1.10. Dispense Vaccination Diary

The investigator or delegate will train the subject or subject's parent/legal guardian in the use of the vaccination diary prior to dispensing it at Visit 1. Oral temperatures, injection-site AEs, prompted systemic complaints, other complaints or illnesses, and medications will be recorded in the vaccination diary throughout the study. The study site personnel will review the data captured in the vaccination diary with the subject at Visit 2 through Visit 4.

3.1.11. Blinding/Unblinding

Not applicable. This is an open-label study.

3.1.12. General Precautions for Administration of Study Vaccines

Adequate treatment provisions, including epinephrine, should be available for immediate use should any anaphylactic or anaphylactoid reactions occur. The subject should stay at least 15 minutes at the investigator's office to detect any immediate AE. A sterile syringe and needle should be used for the vaccination injection for each subject. Needles should not be recapped. Safe disposal procedures should be followed.

3.2 Discontinuation/Withdrawal Criteria

3.2.1. Discontinuation of Vaccination

Discontinuation of study vaccination does not represent withdrawal from the study.

As certain data on clinical events beyond study vaccination discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study vaccination. Therefore, all participants who discontinue study vaccination prior to completion of the vaccination period, will still continue to participate in the trial.

Participants may discontinue study vaccination at any time for any reason or be dropped from the study vaccination at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study vaccination by the investigator if study vaccination is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study vaccination but continue to be monitored in the study for any of the following reasons:

- The participant requests to discontinue study vaccination.

For participants who are discontinued from study vaccination but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed , except for serum collection for HPV testing at the final visit.

Participants may be allowed to begin study vaccination again if deemed medically appropriate.

3.2.2. Withdrawal from the Study

A participant must be withdrawn from the study if the participant withdraws consent from the study. If a participant withdraws from the study, they will no longer receive study vaccination or be followed at scheduled protocol visits. When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed except for serum collection for HPV testing at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 3.4.2 - Assessing and Recording Adverse Events.

3.2.3. Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counselled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

3.3 Immunogenicity Measurements

The assay used in this study is the 9-valent HPV cLIA. The purpose of the assay is to detect antibodies to HPV VLPs types 6, 11, 16, 18, 31, 33, 45, 52, and 58, before and after vaccination with GARDASIL®9. Tests will be performed by Focus Diagnostics, Inc. (California, U.S.A) to measure HPV antibodies at baseline and evaluate the serological response after vaccination. Yeast-derived VLPs are coupled to a set of 9 distinct fluorescent Luminex microspheres. Antibody titres are determined in a multiplexed, competitive format in which known HPV type-specific, phycoerythrin-labelled, neutralising monoclonal antibodies (mAbs) compete with the subject's serum antibodies for binding to type-specific conformationally sensitive, neutralizing epitopes on the VLPs. The fluorescent signals from the bound

HPV –specific detection mAbs are inversely proportional to the subject's neutralizing antibody titres. Results for the assay are reported as a concentration of antibody in arbitrary milli-Merck Units per millilitre (mMU/mL). The HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA is performed in a 96-well microtitre plate. A 12-point standard curve using reference serum pool from adult females immunized with 9 -vHPV vaccine, 4 controls, and 16 samples are added to the plate in duplicate. Samples are tested at a 1:4 and a 1:40 dilution. The detection antibodies followed by the VLP-microspheres for types 6, 11, 16, 18, 31, 33, 45, 52, and 58 are added to each well. The plates are sealed with foil covers and incubated for 15 to 25 hours. Following incubation, the plates are washed and then analysed on a BioPlex (Luminex) instrument. The seropositivity cutoffs for HPV types are assessed using a panel of sera from subjects that are highly likely to be HPV naïve (children), and from subjects who are likely to be seropositive. Any sample being tested for a specific HPV type with a cLIA titre lower than the cutoff corresponding to that HPV type is considered seronegative for that HPV type.

3.4 Safety Measurements

3.4.1 Clinical Measurements for Safety

All subjects will be observed for at least 15 minutes after each study vaccination for any untoward effects, including allergic reactions. This observation period will be documented in the individual subject's source documents.

Each subject will receive a vaccination diary at the Day 1, Month 2, and Month 6 study vaccination visits. In the vaccination diary, the subject will be asked to record oral temperature in the evening after each study vaccination and daily, at the same time of day, for 4 days after each study vaccination for the purpose of identifying febrile events. They will also be asked to record any injection-site reactions prompted in the vaccination diary, i.e., injection-site tenderness, swelling, or redness occurring after each study vaccination and daily for 4 days after each study vaccination (solicited injection-site reactions). In addition to injection-site reactions prompted in the vaccination diary, the subject will be asked to assess the presence of other injection-site reactions and systemic AEs starting after each study vaccination for a total of 15 days. The subject will be asked to record injection-site and systemic AEs, concomitant medications, and concomitant vaccinations on the vaccination diary.

The information on the vaccination diary should be generated only by the subject. The subject will be expected to bring the vaccination diary to the study site at the next scheduled visit. In case of hospitalization or visit to another physician, the subject should be informed to contact the investigator immediately.

The study site personnel will review the data captured in the vaccination diary with the subject or subject's parent/legal guardian at Visit 2 through Visit 4.

All vaccination diary information will be recorded in the individual subject's CRF. The investigator/sub-investigator will determine causality of systemic AEs recorded on the vaccination diary using the guidelines given in Section 3.4.2.4 and will classify each event as an SAE or non-serious AE. If an oral

temperature indicates a fever (defined as an oral temperature of ≥37.8°C), the AE of “fever” must be documented in the individual subject’s CRF.

At the time of vaccination diary review at the next scheduled visit, subjects will be questioned regarding any new medical conditions that occurred beyond Day 15 (after dosing). The investigator/sub-investigator will determine if the medical condition is to be reported as an SAE using the reporting guidelines provided below.

3.4.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. 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 a medicinal product or protocol - specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study vaccine, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Adverse events may occur during the course of the use of the study vaccine during the clinical trial or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre -allocation baseline period as a result of a protocol-specified intervention or a procedure.

All adverse events will be collected from the time the consent form is signed through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, and such events will be recorded at each examination on the Adverse Event case report forms/worksheets.

3.4.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than 0.75 mL of vaccine in any one dose or receiving >4 doses (0.5mL each dose).

If an adverse event(s) is associated with (“results from”) the overdose of the study vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of study vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an adverse event must be reported within 24 hours to MSD either by electronic media or paper.

3.4.2.2 Reporting of Pregnancy and Lactation to MSD

Although not considered an adverse event, it is the responsibility of the investigators or their designees to report any pregnancy in a subject (spontaneously reported to them or detected by urine or serum pregnancy test per protocol) that occurs during the trial through 1 month following the last vaccination. If a subject becomes pregnant during the trial, including subjects who never received vaccine allocation and had a positive pregnancy test at Day 1, all related information must be reported to MSD. For subjects who become pregnant with LMP prior or equal to Day 30 following the final vaccination, the pregnancy will be collected in MSD's global safety database. Furthermore, all fetal loss pregnancy outcomes (ectopic pregnancy, elective termination, spontaneous abortion, late fetal death) must be reported as a Serious Adverse Experience (Other Important Medical Event). All subjects who receive study vaccine, including discontinued subjects who agree to provide further information, must be followed to the completion/termination of the pregnancy. In addition, if the pregnancy continues to term, the outcome (health of the infant) must be reported. If a subject receives study vaccine while breastfeeding all related information, including outcome, must be reported to MSD. Infant serious adverse experiences (SAEs) for all infants born to subjects who received study vaccine must be reported to the MSD.

All pregnancy, lactation, and infant SAE events must be reported within 24 hours to MSD either by electronic media or paper. MSD contact information can be found in the Investigator Trial File Binder. Refer to Data Entry Guidelines (DEGs) for instructions for reporting these events.

3.4.2.3 Immediate Reporting of Adverse Events to the Sponsor

3.4.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of the study vaccine that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a cancer;
- Is associated with an overdose;
- Is another important medical event

Refer to Table 3 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject from the time the consent is signed through 1 month following the last vaccination, whether or not related to the study vaccine, must be reported within 24 hours to MSD either

by electronic media or paper. MSD's contact information can be found in the Investigator Trial File Binder.

Additionally, any serious adverse event brought to the attention of an investigator who is a qualified physician at any time outside of the time period specified in the previous paragraph also must be reported immediately to MSD if the event is either:

- A death that resulted in the subject discontinuing the trial or
- A serious adverse event that is considered by an investigator who is a qualified physician to be vaccine related. All subjects with serious adverse events must be followed up for outcome.

3.4.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to MSD either by electronic media or paper. MSD's contact information can be found in the Investigator Trial File Binder.

Events of clinical interest for this trial include:

- An overdose of study vaccine, as defined in Section 3.4.2.1- Definition of an Overdose for This Protocol and Reporting of Overdose to MSD, that is not associated with clinical symptoms or abnormal laboratory results.

3.4.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 3.The investigator's assessment of causality is required for each adverse event. Refer to Table 3 for instructions in evaluating adverse events.

Table 3: Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities) **Injection site redness or swelling from the day of vaccination through Day 4 post-vaccination will be evaluated by maximum size.**
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose that:	
	†Results in death; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a pre-existing condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when,based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse event? The determination of the likelihood that the test vaccine caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse event based upon the available	

	information. **The following components are to be used to assess the relationship between the test vaccine and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g., diary), seroconversion or identification of vaccine virus in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine? Is the time of onset of the AE compatible with a vaccine-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject reexposed to the test vaccine in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose vaccine trial.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**	

Yes, there is a reasonable possibility of vaccine relationship	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to the administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause.
No, there is not a reasonable possibility of vaccine relationship	Subject did not receive the test vaccine OR temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

3.4.2.5 Sponsor Responsibility for Reporting Adverse Events and Patient/Device Events and Incidents

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

3.5 Statistical analysis plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to database lock, changes are made to primary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Conference on Harmonisation [ICH] Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the clinical study report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. All statistical analyses specified in this protocol will be conducted using R. version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2013).

3.5.1 In-house Blinding

All subjects in this study will receive GARDASIL®9; the study is thus open-label.

3.5.2 Hypothesis/Estimation

Objectives and hypotheses of the study are stated in Section 2.1.

3.5.3 Analysis Endpoints

3.5.3.1 Immunogenicity

The immunogenicity endpoints are:

- The cLIA GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 4 weeks after Dose 3.
- The cLIA seroconversion percentages to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 by 4 weeks after Dose 3.

A subject with a cLIA titre at or above the serostatus cutoff for a given HPV type (see Section 3.3) is considered seropositive for that type. Seroconversion is defined as changing serostatus from seronegative at Day 1 to seropositive, by 4 weeks after Dose 3.

3.5.3.2 Safety

Safety assessment will focus on injection-site adverse reactions and elevated temperatures Day 1 to Day 5 post-vaccination and systemic AEs Day 1 to Day 15 post-vaccination, reported on the vaccination diary. In addition, SAEs and pregnancy will be collected from the time the ICF is signed through 1 month following the last vaccination.

3.5.4 Analysis Populations

3.5.4.1 Immunogenicity Analysis Populations

Per Protocol Immunogenicity Population

The per-protocol immunogenicity (PPI) analysis populations will serve as the primary populations of subjects for the analysis of immune responses to each of the 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58). The PPI analysis populations are HPV type-specific, i.e., each HPV type has its own PPI analysis population. To be included in a particular HPV type-specific PPI analysis population, subjects must:

- Have received all 3 vaccinations of the correct dose of GARDASIL®9 within acceptable day ranges (See Table 4).
- Have evaluable serology results at Day 1 and Month 7 based on serum samples collected within acceptable day ranges (See Table 5).
- Be seronegative to the appropriate HPV type at Day 1.
- Have no protocol deviations that could interfere with the evaluation of subject's immune response to GARDASIL®9.

To be included in the PPI analysis population for any vaccine HPV type, subjects need to be seronegative to that specific type at Day 1. The final determination of protocol deviation categories deemed as having potential to interfere with evaluation of immune response to GARDASIL®9 will be made prior to database lock and will be recorded in a separate study document.

Table 4: Acceptable Day ranges for Vaccination Visits

Dose of 9vHPV Vaccine Scheduled for Injection	Protocol Specified Visit Window for SOT group	Day Range for Inclusion in Statistical Analysis for SOT group (Relative to Day 1†)	Protocol Specified Visit Window for HIV group	Day Range for Inclusion in Statistical Analysis for HIV group (Relative to Day 1†)
Dose 1	Day 1†	0	Day 1†	0
Dose 2	Month 2 ± 4 weeks	30 to 90	Month 2 (-4 weeks / +2 weeks)	30 to 75
Dose 3	Month 6 (-1 week / +4 weeks)	170 to 210	Month 6 ± 4 weeks	150 to 210

† Day 1 refers to the date when Dose 1 of the study vaccine is injected. For vaccinations after Day 1, the day ranges for inclusion in the statistical analysis are wider than the protocol-specified visit windows primarily to account for differences at the study sites in counting months (e.g., 1 calendar month versus 30 days versus 4 weeks).

9vHPV, 9-valent human papillomavirus.

Table 5: Acceptable Day Ranges for Collection of Serum Samples

Study Visit	Target Collection Day (Relative to Day 1†)	Day Range for Inclusion in Statistical Analysis†
Day 1	0	–14 to 0 (Relative to Day 1)‡
Month 7	30 days after Dose 3	21 to 49 after Dose 3§

† Day 1 refers to the date when dose 1 of study vaccine is injected. For Month 7, indicated target collection/day range is relative to date of injection of Dose 3 of study vaccine.

‡ Applies to both the PPI and ANSS analysis populations.

§ Applies to the PPI analysis population only. The day range for the ANSS analysis population is 21 to 105 days after dose 3.

ANSS = All type-specific naïve subjects with serology; PPI = Per-protocol immunogenicity.

<u>All Type-Specific Naïve Subjects with Serology Population</u>

A supportive immunogenicity analysis will be carried out on the all type-specific naïve subjects with serology (ANSS) analysis population. The ANSS analysis populations are HPV type-specific similar to the PPI analysis populations. To be included in these sets of subjects, subjects must:

- Have received all 3 vaccinations of GARDASIL®9;
- Have evaluable serology results at Day 1 and Month 7 based on serum samples collected within acceptable day ranges (See Table 5);
- Be seronegative to the appropriate HPV type at Day 1.

To be included in the ANSS analysis population for HPV 6 and 11, subjects must be seronegative to both HPV 6 and 11 at Day 1. To be included in the ANSS analysis population for any other vaccine HPV type, subjects need to be seronegative to that specific type at Day 1.

Unlike the PPI analysis populations, ANSS analysis populations will not exclude subjects who had protocol deviations deemed as having potential to interfere with evaluation of immune response to GARDASIL®9. In addition, no day ranges on the timing of the vaccination will be applied.

<u>The seropositive or GMT population</u>

The seropositive or GMT analysis population will include subjects who were seropositive at day 1 for a given HPV type. An increase in antibody titers pre- and postvaccination will be analysed for each of the 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58). The seropositive analysis populations are HPV type-specific, i.e., each HPV type has its own seropositive analysis population. To be included in a particular HPV type-specific seropositive analysis population, subjects must:

- Have received all 3 vaccinations of the correct dose of GARDASIL®9 within acceptable day ranges (See Table 4).

- Have evaluable serology results at Day 1 and Month 7 based on serum samples collected within acceptable day ranges (See Table 5).
- Be seropositive to the appropriate HPV type at Day 1.
- Have no protocol deviations that could interfere with the evaluation of subject's immune response to GARDASIL®9.

3.5.4.2 Safety Analysis Population

The all subjects as-treated (ASaT) analysis population, comprised of subjects who received at least 1 dose of GARDASIL®9 and had at least 1 study visit with safety follow-up, will be the primary population for safety analyses.

3.5.5 Statistical Methods

3.5.5.1 Immunogenicity Analyses

The primary analyses of immunogenicity will be conducted in the Per Protocol Immunogenicity (PPI) population as defined in Section 3.5.4.1. Immunogenicity data will be analysed separately for HIV and SOT patients. The potential influence of factors such as immunosuppressive therapy and time after transplantation for SOT patients and CD4-count and antiretroviral therapy for HIV patients will be estimated.

- Seroconversion

The primary outcome, seroconversion, defined as changing serostatus from seronegative at Day 1 to seropositive (antibody titre above seroconversion cut-off) by 4 weeks after Dose 3, will be described with 95% CI. Differences with historical controls will be determined with a test for binary (seroconversion or not) proportions.

- GMT

All titers will be log transformed and the antilog of the mean will be calculated to obtain the GMT. GMT will be described with 95%CI. GMTs of immunocompromised patients will be compared with GMTs of historical controls with a one sample *t*-test, comparing month 7 GMTs for each component.

3.5.5.2 Statistical Methods for Safety Analyses

All subjects who received at least 1 dose of GARDASIL®9 and have safety follow-up data will be included in the analysis of safety.

Prevalence of safety measures will be described with 95% CI and will be compared to the prevalence in historical controls with a test for proportions. Regardless of incidence, all AEs will be summarized as frequencies and percentages by vaccination visit, and across all vaccination visits. Specific AEs for which summaries will be provided are identified in Table 6. Incidence is defined as (number of subjects

with the indicated endpoint divided by the total number of subjects with follow-up over the relevant period) × 100%. Confidence intervals (95%) and 2-sided p-values will be provided without adjusting for multiplicity. Treatment administration data will be summarized for including number of vaccine injections received. Imputation methods will not be used to replace missing safety data. Safety data for HIV patients and SOT patients will be analysed separately.

Table 6: Analysis Strategy for Safety Parameters

Adverse Event Endpoint	Follow-Up Period			Summaries/Analyses		
	After Any Vaccination Visit		Any Time During Study	Incidence	Risk Difference and 95% CI (b)	p-Value
	Day 1 to Day 5 (a)	Day 1 to Day 15 (a)				
Clinical AE						
• Any AE		•		•		
• Death			•	•		
• Injection-site adverse events (c)						
• Injection-site pain/tenderness,swelling, and redness	•			•	•	•
• Other injection-site adverse reactions	•			•	• (d)	
• Severe injection-site adverse reactions	•			•	•	
• Number (%) of subjects by maximum intensity rating, over all injection-site adverse reactions	•			•		
• Number (%) of subjects by maximum intensity rating, within each of the categories of injection-site adverse reactions	•			•		
Systemic AEs						
• Systemic AEs		•		•	• (e)	
• Number (%) of subjects by maximum intensity rating, over all systemic AEs		•		•		
Temperatures						
Elevated temperatures (f)	•			•	•	•
Maximum temperatures (g)	•			•		

AEs of special interest						
• Serious AEs • Serious VR AEs • New medical conditions		•	 • •	• • •	•	

(a) The day of vaccination is counted as Day 1.

(b) Defined as the difference in incidence between the comparison groups (SOT and HIV patients versus historical controls).

(c) For the injection-site redness and swelling 0 to 2.5 cm (0 to 1 inch) will be categorized as mild, >2.5 to 5 cm (>1 inch to 2 inches) will be categorized as moderate, and >5 cm (>2 inches) will be categorized as severe.

(d) Only for injection-site adverse reactions occurring in ≥1% of subjects in either group.

(e) Only for systemic AEs occurring in ≥1% of subjects in either group.

(f) Defined as maximum (over the follow-up period) temperature ≥37.8°C.

(g) Distribution of maximum temperatures over the relevant follow-up period.

AEs, adverse events; VR, vaccine-related.

3.5.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics and demographic variables will be summarized for HIV and SOT patients using descriptive statistics or categorical tables on all subjects enrolled in the study and on all PPI eligible subjects (i.e., subjects belonging to at least one PPI analysis populations). No formal statistical testing of differences with census data from patient populations with respect to these characteristics will be performed.

Quantitative variables (except antibody titres) will be displayed using descriptive statistics by way of sample size, mean, standard deviation, median, minimum, and maximum. Antibody titres will be displayed using descriptive statistics by way of sample size, GMT s, and two-sided 95% CIs.

Categorical variables will be displayed using descriptive statistics by way of sample size, count by category, and proportion by category. Missing data will be counted but not included in the calculation of proportions.

Subject Accounting

The number and percentage of subjects screened (ICF signed), enrolled (allocation number assigned), vaccinated (at least once and at each vaccination time point), discontinued, and the primary reason for discontinuation will be displayed for HIV and SOT patients. Reasons for subjects excluded from the PPI analysis populations will be summarized and displayed in subject accounting tables.

Subject Characteristics

Demographic variables and other baseline characteristics such as age, vital signs (height, weight, and oral temperature), and country of origin will be summarized for both HIV and SOT patients.

Baseline HPV Status

A serum sample will be collected from all subjects at the Day 1 visit for the purpose of assessing baseline HPV serostatus to the 9vHPVvaccine HPV types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58). A subject will be considered seropositive to a given HPV type at Day 1 if the subject's anti-HPV titre is greater than or equal to the corresponding serostatus cutoff for that HPV type or seronegative to a given HPV type at Day 1 if the subject's anti-HPV titre is less than the corresponding serostatus cutoff for that HPV type. For each HPV type, the proportions of subjects who are seronegative or seropositive will be summarized for both HIV and SOT patients.

Prior and Concomitant Medications

The number and percentage of subjects with prior medications or vaccinations prior to each study vaccination will be summarized for both HIV and SOT patients. The relevant pre-injection day ranges for summarization will be 3 days for medications, 14 days for non-live virus vaccines, and 28 days for live virus vaccines.

Similarly, the number and percentage of subjects with concomitant medications or vaccinations within 15 days (Day 1 to Day 15) following any study vaccination will be summarized for each age group. The number of subjects with "Special Medications" (corticosteroids, immunosuppressives, immune globulins, and blood products [Section3.2.4]) will be summarized for both HIV and SOT patients throughout the study period.

New Medical Conditions: New medical conditions occurring during the study (i.e., incident medical conditions occurring outside of a Day 1 to Day 15 period post -vaccination and not considered SAEs) will be summarized for both HIV and SOT patients.

3.5.6 Sample Size and Power Calculations

Based on an expected seroconversion rate of 80%, a sample size of 170 transplant patients allows to estimate the proportion of protected transplant patients with precision (95% confidence interval) of ±6% (10).

Furthermore, based on an expected seroconversion rate 85-91%, a sample size of 140 HIV-patients allows to estimate the proportion of protected patients with precision (95% confidence interval) of ±6% and 5% respectively (7). Based on expected differences in GMT to healthy populations, a sample size of 140 HIV-patients allows to estimate the GMTs HPV type 6, 11, 16 and 18 with a power of 0.38, 0.82, 1 and 1, respectively (7, 19).

Due to difficulties in the recruitment of HIV patients without genital warts a recalculation of the sample size was done. With a total sample size of n=100, a majority of whom will have no history of HPV-lesions, we expect to be able to use the data of at least 80 patients for the analysis seroconversion of each HPV type under study. Seroconversion rates of 95-99% for HPV types 6, 11 and 16 can then be

estimated with a margin of error of ±4.8% - 2.2%, and the anticipated seroconversion rate of 90% for HPV type 18 with a margin of error of ±6.6%.

3.5.7 Interim Analysis

No interim analysis is planned.

3.6 DEFINITION OF COMPLIANCE MEASURE

Compliance is defined in this study as receipt of all scheduled study vaccinations. To summarise compliance, the numbers of subjects who receive each vaccination will be tabulated. Compliance with the planned vaccination schedule (Day 1, Month 2, and Month 6) will be described by histograms of actual intervals between vaccinations relative to the expected interval in the CSR.

3.7 Labeling, Packaging, Storage, Dispensing, and Return of Clinical Supplies

3.7.1 Product Description

Investigational Medicinal Product (IMP) will be provided by MSD as summarized in

Table 7.

Table 7: Investigational medicinal product

Product name	Potency	Dosage Form/ Content s/ Route of Administration	Storage Conditions
GARDASIL®9 V503 (9-Valent HPV L1 VLP) Vaccine (Recombinant, adsorbed)	**HPV Types (L1 protein)** **6/11/16/18/31/33/45/52/58** 30/40/60/40/20/20/20/20/20 mcg Adsorbed on AAHS 500 mcg	Sterile suspension for intramuscular injection 1 dose (0.5 mL) Shake well before use.	Store at 2.0 to 8.0°C Do not freeze. Protect from light.
AAHS, Merck Aluminum Adjuvant (amorphous aluminum hydroxyphosphate sulfate); HPV, human papillomavirus; VLP, virus-like particle.			

GARDASIL®9 is available as a suspension for injection. It appears as a clear liquid with white precipitate.

3.7.2 Packaging Information

Supplies will be labelled in accordance with local regulatory requirements.

3.7.3 Clinical Supplies Disclosure

Not applicable. This study is open-label.

3.7.4 Shipment of Investigational Medicinal Product

The IMP will be shipped to the study site, refrigerated and stored at 2.0°C to 8.0°C following the guidelines on transport on commercial goods. Upon receipt at the study site, the vaccine should be removed from the outer secondary shipping box and placed immediately into the refrigerator.

Upon arrival of the shipment at the study site, the person responsible will verify that the content of the shipment corresponds to the order and that the products arrived in good condition. He/she will acknowledge receipt to MSD Belgium by email.

3.7.5 Storage and Handling Requirements

The clinical supplies storage area at the study site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained. Supplies should be stored in the original nested box with the lid closed to minimize exposure to light. If the refrigerator in which the study vaccine is stored deviates from the 2.0°C to 8.0°C range, study vaccinations should be suspended and MSD should be contacted immediately. Vaccine must NOT be frozen.

A daily refrigerator temperature log must be maintained at the study site. The refrigerator must be equipped with an appropriately calibrated min/max thermometer and/or circular chart temperature recorder. The temperature log will be reviewed by the investigator (or designee). An appropriate back up system (i.e., alarm or generator) and study site personnel telephone numbers should be in place in the event of a refrigerator failure.

In case of a cold chain break (i.e., if the temperature of the refrigerator is lower than 2.0°C or exceeds 8.0°C):

- The investigator (or designee) at the site should follow the current clinical complaint process to file an excursion
- The investigator (or designee) must wait for further instructions from MSD, as to whether or not the study vaccines can be used. The investigator is not allowed to use the study vaccines before getting MSD approval to do so.
- The cold chain break must be documented in the Investigator site file and the Trial Master File.

The IMP must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. IMP is to be administered only in accordance with the protocol.

Any concerns raised about the manufacturing, packaging, labelling, or distribution of IMP supply which could potentially impact its suitability for use should be immediately reported to MSD. The IMP must be quarantined until the MSD's feed-back is received as to whether or not the vaccine can be used.

Unused study vaccines taken out from the stock at study site are considered to be unusable and cannot be returned to the stock. They must be quarantined and returned back to MSD as soon as possible.

3.7.6 Accountability of Investigational Medicinal Product

For the accountability procedure, please refer to Guidelines for IMP Management on site.

3.7.7 Return of Investigational Medicinal Product

All empty primary containers will be destroyed at the study site according to local regulations. Supplies will need to be returned to the depot of origin if destruction is not possible locally.

Empty boxes of study vaccines must be kept at study site to enable verification of the vaccine accountability and can be destroyed on site after study has been completed. The following should be returned to the distributor according to the procedures detailed in the Investigator Site File:

- Study vaccines unusable following a cold chain deviation, as soon as possible;
- Study vaccines expiring within the current month, immediately;
- Unused study vaccines which remain in stock at study site after the last administration to the last subject of the corresponding study site, after verification of vaccine accountability;
- Study vaccines concerned by a batch recall, immediately.

For the return procedure, please refer to Guidelines for IMP Management on site. The distributor will confirm the receipt of each study vaccine returned (at unit level).

3.8 Data Management

Study data will be acquired via electronic format. As part of their responsibilities, the principal investigator or sub-investigator agree to maintain adequate source documents for the subjects treated as part of the research under this protocol. The principal investigator or sub-investigator agree to maintain source documentation (e.g., laboratory reports), to enter subject data into the individual subject's CRF as accurately as possible.

Each CRF will allow data entry by study site staff that can add and edit data, identify and resolve discrepancies, and view records. This system detection of discrepancies, enabling study site coordinators to resolve and manage discrepancies in a timely manner.

The electronic database will be password protected. A quality review of the data will be performed by the study site by an independent person through risk-based source data verification of essential data.

3.9 Study report

A clinical study report will be provided in which the study results will be compared with historical controls.

4.0. ADMINISTRATIVE AND REGULATORY DETAILS

4.1. Confidentiality

4.1.1. Confidentiality of Subject Records

By signing this protocol, the investigator agrees that IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; only serum samples will be transmitted to MSD, which will only have a unique code..

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

4.1.2. Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor, in collaboration with the relevant investigator is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

4.2. Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol, ICH GCP guidelines, the EU Clinical Trial Directive (as it may be amended or superseded from time to time), the latest version of the Declaration of Helsinki ; and all applicable federal and local laws, rules and regulations relating to the conduct of the clinical trial.

The investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-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 trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal and local laws, rules and regulations.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. 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. By signing this protocol, the investigator agrees that documentation shall be retained at least 20 years the study was concluded.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform Sponsor of any regulatory authority inspection conducted for this trial. Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this trial. The investigator will immediately disclose in writing to the IRB/IEC if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In addition, the investigator will review the trial report that summarizes the trial results and will describe the conduct and results of the trial [Clinical Study Report (CSR)] accurately to the best of his/her knowledge.

4.3. Compliance with Trial Registration and Results Posting Requirements

Under the terms of the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. The Sponsor of this trial, will review this protocol and submit the information necessary to fulfil these requirements. Sponsor entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information. By signing this protocol, the investigator acknowledges that the statutory obligations under the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

4.4 Quality Management System

By signing this protocol, the Investigator agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

4.5 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data.

4.6 Publications

This trial is intended for publication. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The authors will submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. The investigator will post a synopsis of trial results on www.clinicaltrials.gov by 12 months after the last data have become available . Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript. MSD will receive the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 30 days prior to submission for publication/presentation. Any information identified by the MSD as confidential will be deleted prior to submission; this confidentiality does not include efficacy and safety results. MSD review can be expedited to meet publication timelines.

5.0 LIST OF REFERENCES

1. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine. 2006;24 Suppl 3:S3/11-25.
2. Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. Jama. 2001;285(23):2995-3002.
3. Moscicki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. J Pediatr. 1998;132(2):277-84.
4. Moscicki AB, Ellenberg JH, Crowley-Nowick P, Darragh TM, Xu J, Fahrat S. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. J Infect Dis. 2004;190(8):1413-21.
5. Weinberg A, Song LY, Saah A, Brown M, Moscicki AB, Meyer WA, 3rd, et al. Humoral, mucosal, and cell-mediated immunity against vaccine and nonvaccine genotypes after administration of quadrivalent human papillomavirus vaccine to HIV-infected children. J Infect Dis. 2012;206(8):1309-18.
6. Kahn JA, Xu J, Kapogiannis BG, Rudy B, Gonin R, Liu N, et al. Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women. Clin Infect Dis. 2013;57(5):735-44.
7. Kojic EM, Kang M, Cespedes MS, Umbleja T, Godfrey C, Allen RT, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis. 2014;59(1):127-35.
8. Denny L, Hendricks B, Gordon C, Thomas F, Hezareh M, Dobbelaere K, et al. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. Vaccine. 2013;31(48):5745-53.
9. MacIntyre CR, Shaw P, Mackie FE, Boros C, Marshall H, Barnes M, et al. Immunogenicity and persistence of immunity of a quadrivalent Human Papillomavirus (HPV) vaccine in immunocompromised children. Vaccine. 2016;34(36):4343-50.
10. Kumar D, Unger ER, Panicker G, Medvedev P, Wilson L, Humar A. Immunogenicity of quadrivalent human papillomavirus vaccine in organ transplant recipients. Am J Transplant. 2013;13(9):2411-7.
11. Gomez-Lobo V, Whyte T, Kaufman S, Torres C, Moudgil A. Immunogenicity of a prophylactic quadrivalent human papillomavirus L1 virus-like particle vaccine in male and female adolescent transplant recipients. Pediatr Transplant. 2014;18(3):310-5.
12. Levin MJ, Moscicki AB, Song LY, Fenton T, Meyer WA, 3rd, Read JS, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. J Acquir Immune Defic Syndr. 2010;55(2):197-204.
13. Toft L, Tolstrup M, Muller M, Sehr P, Bonde J, Storgaard M, et al. Comparison of the immunogenicity of Cervarix(R) and Gardasil(R) human papillomavirus vaccines for oncogenic non-vaccine serotypes HPV-31, HPV-33, and HPV-45 in HIV-infected adults. Hum Vaccin Immunother. 2014;10(5):1147-54.
14. Zhai L, Tumban E. Gardasil-9: A global survey of projected efficacy. Antiviral Res. 2016;130:101-9.
15. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711-23.
16. Luxembourg A, Moreira ED, Jr., Samakoses R, Kim KH, Sun X, Maansson R, et al. Phase III, randomized controlled trial in girls 9-15 years old to evaluate lot consistency of a novel nine-valent human papillomavirus L1 virus-like particle vaccine. Hum Vaccin Immunother. 2015;11(6):1306-12.
17. Vesikari T, Brodszki N, van Damme P, Diez-Domingo J, Icardi G, Petersen LK, et al. A Randomized, Double-Blind, Phase III Study of the Immunogenicity and Safety of a 9-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine (V503) Versus Gardasil(R) in 9-15-Year-Old Girls. Pediatr Infect Dis J. 2015;34(9):992-8.
18. Van Damme P, Meijer CJ, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, et al. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016;34(35):4205-12.
19. Castellsague X, Munoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer. 2011;105(1):28-37.

6.0 SIGNATURES

As principal investigator, I agree to conduct this clinical trial 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). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical 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 events as defined in Section 3.4.2 – TRIAL PROCEDURES (Assessing and Recording Adverse Events) to MSD. I also agree to handle all study vaccines provided by MSD and collect and handle all clinical specimens in accordance with the protocol.

Name Principal Investigator	
Title	
Signature	
Date signed	