PROTOCOL TITLE

Prospective analysis of immunogenicity of the nanovalent human papillomavirus vaccination (GARDASIL 9) in patients pre and post solid organ transplant.

Protocol Number
MISP 61451

Version 1.2

Date
July 19, 2022

Regulatory Sponsor:	Medical College of Wisconsin Department of Ob/Gyn, Division of Gynecologic Oncology 9200 West Wisconsin Avenue, Milwaukee, WI 53226 414-805-6606
Funding Sponsor:	Merck Investigator Initiated Studies Program
Study Product:	Human Papillomavirus 9-valent Vaccine, Recombinant. GARDASIL 9

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List of Abbreviations

9vHPV, HPV9	Nanovalent HPV; GARDASIL 9 vaccine
AE	Adverse Event
AST	American Society of Transplantation
CDC	Centers for Disease Control and Prevention
cLIA	Competitive Luminex Immunoassay
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
4vHPV	Quadrivalent HPV; GARDASIL vaccine
GMT	Geometric Mean Titers
HPV	Human papillomavirus
IDS	Investigational Drug Services
IM	Intramuscular
mMU	milli-Merck Units
SAE	Serious Adverse Event

Study Summary

Title	Prospective observational analysis of the immunogenicity of the nanovalent human papillomavirus vaccination (GARDASIL 9) in patients pre and post solid organ transplant.
Short Title	Immunogenicity of HPV vaccine in transplant recipients
Protocol Number	MISP 61451
Phase	N/A
Methodology	Prospective cohort, open-label, non-randomized observational study
Study Duration	36 months
Study Center(s)	Single center
Objectives	Determine the immunogenicity of 9vHPV vaccine in patients pre and post renal transplant.
Number of Subjects	100
Diagnosis and Main Inclusion Criteria	Nanovalent HPV vaccination (GARDASIL 9) in patients $\leq$ 45 yo prior to or > 3 months post renal transplant.
Study Product, Dose, Route, Regimen	GARDASIL 9 Vaccination IM Administration
Duration of administration	Drug administration in 3 doses at 0, 2 and 6 months
Reference therapy	N/A
Statistical Methodology	Basic demographic and clinical characteristics will be collected and presented with descriptive statistics. Chi-square or Fischer's exact test to be used for between group comparisons of categorical variables, and Mann-Whitney U-test to be used for continuous variables. Logistic regression analysis will be used to evaluate factors influencing seroconversion. Mixed effect linear regression models will be used to estimate and compare mean titers between groups and within groups over time.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States (1). HPV is responsible for causing nearly all cervical cancers and most vaginal, vulvar, anal, rectal, penile, and oropharyngeal cancers. According to the Centers of Disease Control and Prevention (CDC), each year, more than 35,000 cancers are attributed to HPV infection [1]. Primary prevention of HPV infection with vaccination remains the most effective strategy to reduce HPV associated cancers and pre-cancers.

The first HPV vaccinations (GARDASIL quadrivalent HPV vaccine /4vHPV and Cervarix) were FDA approved for use in 2006. The current nanovalent HPV (9vHPV/ GARDASIL 9) vaccine provides protection from HPV-related infections from HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58. Current recommendations approve the administration of the 9vHPV in people up to age 45 with appropriate shared decision-making pertaining to individual risk factors. The 9vHPV vaccine is a recombinant vaccination approved for administration in immunosuppressed individuals.

Premalignancy and malignancy post solid organ transplantation is a major concern in transplant medicine and a well-documented risk of organ transplantation. The reduced kidney function and uremia associated with chronic kidney disease and end stage renal disease are associated with alterations in the immune system and an increased risk of neoplastic diseases [4]. Incidence of malignancy in renal transplant recipients is reported as 3-5 times greater than the general population [2,3]. Specifically, premalignancies and malignancies related to HPV viral infections disproportionately affect transplant recipients as compared to healthy controls making this a very high-risk population in need of evidence-based strategies to decrease morbidity and mortality [5,6,7].

Due to marked improvements in transplant medicine, grafts are functional longer, solid organ recipients live longer, receive immunosuppressant medications longer and are candidates for transplantation at even older ages. This longevity, however, exposes individuals to a greater risk of infections such as HPV and neoplastic processes as well. Addressing strategies to prevent premalignancy and malignancy in this population needs to become a priority [8].

Limited data are available on the immunogenicity of the 4vHPV vaccine in this population. In one study by Kumar et al [9], 47 patients post-transplant ages 18-35 were given three-doses of 4vHPV vaccine and response was observed. The response rate to at least one of the HPV vaccine subtypes was 61%. Response to all four HPV vaccine subtypes was 47% but waned over time with a significant decrease in HPV immunogenicity noted at 1 year post enrollment. No significant change in seropositivity of patients was noted after 1 year. A similar study in patients

9-21 years showed antibody responses ranging from 33-80% depending on HPV type. A systematic literature search was performed in a 2019 study by Vinkenes et al [12] to identify solid organ transplant patients who received HPV vaccination. They found only 3 cohort studies looking at HPV immunogenicity. Two studies (Nelson et al. and Kumar et al. with less than 50 patients in each study) found a suboptimal effect of the quadrivalent HPV vaccine. In contrast, the third study (Gomez –Lobo et al [13]) found high antibody response in 100% of its 8 patients to all four HPV genotypes in the quadrivalent HPV vaccine. It is important to note that there were no severe safety signals in the larger studies by Kumar and Nelson. HPV vaccination is assumed to be safe since it is an inactivated vaccine. Gomez –Lobo et al. noted increased acute rejection in their study of 8 patients but could not conclude an association with the HPV vaccine. No data in the transplant setting are available for the 9vHPV/ GARDASIL 9 vaccination.

We propose an evaluation of 9vHPV vaccination immunogenicity with serial geometric mean titers (GMTs) in two settings: prior to renal transplant and post-renal transplant. Providing data on the immunogenicity of 9vHPV vaccine may enable stronger recommendations for completion to be made prior to transplant and may provide data on whether obtaining post-vaccination titers is clinically relevant. Determination overtime of the course of the decline of GMTs, what factors (if any) influence that decline, and whether patients change their seropositivity status would be instrumental for counseling patients on the risks and benefits of the HPV vaccination and may be of significant value to other populations that are immunocompromised, such as pediatric immunocompromised individuals or those with HIV.

This data might be the first step in determining whether the timing of vaccination, alternative vaccination schedule, or additional vaccinations in the series could optimize HPV response and reduce HPV infectious morbidity in the transplant population. This could have a major impact on guidelines, such as those from the American Society of Transplantation (AST) recommendations for transplant patients.

Although the decreased prevalence of HPV has been demonstrated since the initiation of vaccination in the immunocompetent population, no such data exist for the transplant population. In the future, we would like to study whether HPV vaccination can impact the subsequent development of premalignancy or malignancy in the solid organ transplant population and help advance the relatively new field of onconephrology. This knowledge might have implications for vaccination, screening, and surveillance recommendations for many other populations that are immunosuppressed as well. We anticipate that a longer follow-up will be needed to determine if HPV morbidity is decreased by HPV vaccination, but we will monitor HPV infectious events during the study.

Many steps to decrease HPV morbidity in transplant patients need further study and so many questions remain: can HPV vaccination prevent cancer in all potential HPV sites (oral, anal, cervical), is there a vaccination strategy that will be cost-effective, will there be immunogenicity in populations that have a high prevalence of HPV exposure such as individuals in older age groups, could different dosages of the vaccine elicit improved responses. Could HPV typing of precancers, or cancers diagnosed in surveillance to see if they were secondary to the HPV types

present in the 9vHPV vaccine and compare that with the patients' serum GMTs to determine if a threshold exists for risk of developing a premalignancy or malignancy. Could it be possible to determine the minimum immunogenicity required to prevent disease?

They HPV related morbidity experienced by immunosuppression in transplant patients represents excessive morbidity and excessive cost that might be able to be impacted by the HPV vaccine. Initial data on this population will be informative for developing strategies to impact outcomes.

1.2 Investigational Agent

GARDASIL 9, Human Papillomavirus 9-valent vaccine, recombinant, is an **FDA approved** non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant Saccharomyces cerevisiae and self-assembled into VLPs. The fermentation process involves growth of S. cerevisiae on chemically defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP (virus like particles) vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer. GARDASIL 9 is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV Type 6 L1 protein, 40 mcg of HPV Type 11 L1 protein, 60 mcg of HPV Type 16 L1 protein, 40 mcg of HPV Type 18 L1 protein, 20 mcg of HPV Type 31 L1 protein, 20 mcg of HPV Type 33 L1 protein, 20 mcg of HPV Type 45 L1 protein, 20 mcg of HPV Type 52 L1 protein, and 20 mcg of HPV Type 58 L1 protein. Each 0.5-mL dose of the vaccine also contains approximately 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant Saccharomyces cerevisiae and self-assembled into VLPs. The fermentation process involves growth of S. cerevisiae on chemically defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates.

After thorough agitation, GARDASIL 9 is a white, cloudy liquid.

HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Efficacy of GARDASIL 9 against anogenital diseases related to the vaccine HPV types in human beings is thought to be mediated by humoral immune responses induced by the vaccine, although the exact mechanism of protection is unknown.

1.3 Clinical Data to Date

Efficacy and/or immunogenicity of the 3-dose regimen of GARDASIL 9 has been assessed in seven clinical trials. Study 1 evaluated the efficacy of GARDASIL 9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL as a comparator. The analysis of efficacy for GARDASIL 9 was evaluated in the per-protocol efficacy (PPE) population of 16- through 26-year-old girls and women, who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were naïve to the relevant HPV type(s) by serology and PCR of cervicovaginal specimens prior to dose one and who remained PCR 15 negative for the relevant HPV type(s) through one month post-dose 3 (Month 7). Overall, approximately 52% of subjects were negative to all vaccine HPV types by both PCR and serology at Day 1. The primary analysis of efficacy against HPV Types 31, 33, 45, 52, and 58 is based on a combined endpoint of Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3, Adenocarcinoma in situ (AIS), invasive cervical carcinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar cancer, or vaginal cancer. Other endpoints evaluated include cervical, vulvar, and vaginal disease of any grade, persistent infection, cytological abnormalities, and invasive procedures. For all endpoints, the efficacy against the HPV Types 31, 33, 45, 52 and 58 in GARDASIL 9 was evaluated compared with GARDASIL. The efficacy of GARDASIL 9 against anal lesions caused by HPV Types 31, 33, 45, 52, and 58 was not assessed due to low incidence. Effectiveness of GARDASIL 9 against anal lesions was inferred from the efficacy of GARDASIL against anal lesions caused by HPV types 6, 11, 16 and 18 in men and antibody responses elicited by GARDASIL 9 against the HPV types covered by the vaccine. Effectiveness against disease caused by HPV Types 6, 11, 16, and 18 was assessed by comparison of geometric mean titers (GMTs) of type-specific antibodies following vaccination with GARDASIL 9 with those following vaccination with GARDASIL (Study 1 and Study 3). The effectiveness of GARDASIL 9 in children 9 through 15 years old and in boys and men 16 through 26 years old was inferred based on a comparison of type-specific antibody GMTs to those of 16 through 26-year-old girls and women following vaccination with GARDASIL 9. Immunogenicity analyses were performed in the per-protocol immunogenicity (PPI) population consisting of individuals who received all three vaccinations within predefined day ranges, did not have major deviations from the study protocol, met pre-defined day range for serum collection for assessment of antibody response and were naïve [PCR negative (in girls and women 16 through 26 years of age; Studies 1 and 2) and seronegative (Studies 1, 2, 3, 5, 7 and 8)] to the relevant HPV type(s) prior to dose 1 and among 16- through 26-year-old girls and women (Studies 1 and 2) remained PCR negative to the relevant HPV type(s) through Month 7. Pre-defined day ranges for vaccinations were relative to Day 1 (dose 1). For the 3-dose schedule, dose 2 was at 2 months (± 3 weeks) and dose 3 was at 6 months (± 4 weeks). For the 2-dose schedule, dose 2 was at 6 or 12 months (± 4 weeks). Pre-defined day range for serum collection for assessment of antibody response was 21 to 49 days after the last dose. Study 1 evaluated immunogenicity of GARDASIL 9 and efficacy to prevent infection and disease caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women. Study 2 evaluated immunogenicity of GARDASIL 9 in children 9 through 15 years of age and women 16 through 26 years of age. Study 3 evaluated immunogenicity of GARDASIL 9 compared with GARDASIL in girls 9 through 15 years of age. Study 4 evaluated administration of

GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL. Study 5 evaluated GARDASIL 9 concomitantly administered with Menactra and Adacel in children 11 through 15 years of age. Together, these five clinical trials evaluated 12,233 individuals who received GARDASIL 9 (8,048 girls and women 16 through 26 years of age at enrollment with a mean age of 21.8 years; 2,927 girls 9 through 15 years of age at enrollment with a mean age of 11.9 years; and 1,258 boys 9 through 15 years of age at enrollment with a mean age of 11.9 years. Study 7 evaluated immunogenicity of GARDASIL 9 in boys and men, including 1,106 self-identified as heterosexual men (HM) and 313 self-identified as men having sex with men (MSM), 16 through 26 years of age at enrollment (mean ages 20.8 years and 22.2 years, respectively) and 1,101 girls and women 16 through 26 years of age at enrollment (mean age 21.3 years). Study 9 evaluated immunogenicity of GARDASIL 9 in 640 women 27 through 45 years of age and 570 girls and women 16 through 26 years of age (mean ages 35.8 years and 21.6 years, respectively). The race distribution of the 16- through 26-year-old girls and women in the clinical trials was as follows: 56.8% White; 25.2% Other; 14.1% Asian; and 3.9% Black. The race distribution of the 9- through 15-year-old girls in the clinical trials was as follows: 60.3% White; 19.3% Other; 13.5% Asian; and 7.0% Black. The race distribution of the 9- through 15-year-old boys in the clinical trials was as follows: 46.6% White; 34.3% Other; 13.3% Asian; and 5.9% Black. The race distribution of the 16- through 26-year-old boys and men in the clinical trials was as follows: 62.1% White; 22.6% Other; 9.8% Asian; and 5.5% Black. In Study 9 the race distribution of 27- through 45-year-old women was as follows: 97.7% White, 1.6% Asian, 0.3% Other or Multiracial, and 0.5% Black. The race distribution of girls and women 16 through 26 16 years of age in this study was as follows: 94.6% White, 3.0% Asian, 1.6% Other or Multiracial, and 0.9% Black. One clinical trial (Study 8) assessed the 2-dose regimen of GARDASIL 9. Study 8 evaluated the immunogenicity of 2 doses of GARDASIL 9 in children 9 through 14 years of age and 3 doses of GARDASIL 9 in girls 9 through 14 years of age and women 16 through 26 years of age; (N=1,518; 753 girls; 451 boys and 314 women). The mean age for the children 9 through 14 years of age was 11.5 years; the mean age for girls and women 16 through 26 years of age was 21.0 years. In Study 8, the race distribution was as follows: 61.1% White; 16.3% Asian; 13.3% Other; and 8.9% Black.

Based on the above clinical data, GARDASIL 9 vaccination is FDA approved in both male and female individuals up to age 45 years.

In the current studies, seropositive is defined as an anti-HPV titer greater than or equal to the pre-specified serostatus cutoff for a given HPV type. Seronegative is defined as an anti-HPV titer less than the prespecified serostatus cutoff for a given HPV type. The serostatus cutoff is the antibody titer level above the assay's lower limit of quantification that reliably distinguishes sera samples classified by clinical likelihood of HPV infection and positive or negative status by previous versions of competitive Luminex Immunoassay (cLIA). The lower limits of quantification and serostatus cutoffs for each of the 9 vaccine HPV types are shown in Table 5 below. PCR positive is defined as DNA (deoxyribonucleic acid) detected for a given HPV type. PCR negative is defined as DNA not detected for a given HPV type. The lower limit of detection for the multiplexed HPV PCR assays ranged from 5 to 34 copies per test across the 9 vaccine HPV types.

Table: Competitive Luminex Immunoassay (cLIA) Limits of Quantification and Serostatus Cutoffs for GARDASIL 9 HPV Types

HPV Type	cLIA Lower Limit of Quantification (mMU*/ mL)	cLIA Serostatus Cutoff (mMU*/ mL)
HPV 6	16	30
HPV 11	6	16
HPV 16	12	20
HPV 18	8	24
HPV 31	4	10
HPV 33	4	8
HPV 45	3	8
HPV 52	3	8
HPV 58	4	8

*mMU=milliMerck Units

The minimum anti-HPV titer that confers protective efficacy has not been determined. Type-specific immunoassays (i.e., cLIA) with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate. Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT). Studies Supporting the Effectiveness of GARDASIL 9 against HPV Types 6, 11, 16, and 18 Effectiveness of GARDASIL 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 was inferred from non-inferiority comparisons in Study 1 (16- through 26-year-old girls and women) and Study 3 (9- through 15-year-old girls) of GMTs following vaccination with GARDASIL 9 with those following vaccination with GARDASIL. A small number of efficacy endpoint cases related to HPV types 6, 18 11, 16 and 18 in both vaccination groups precluded a meaningful assessment of efficacy using disease endpoints associated with these HPV types. The primary analyses were conducted in the per-protocol population, which included subjects who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were HPV-naïve. HPV-naïve individuals were defined as seronegative to the relevant HPV type(s) prior to dose 1 and among female subjects 16 through 26 years of age in Study 1 PCR negative to the relevant HPV type(s) in cervicovaginal specimens prior to dose 1 through Month 7. Anti-HPV 6, 11, 16 and 18 GMTs at Month 7 for GARDASIL 9 among girls 9 through 15 years of age and young women 16 through 26 years of age were non-inferior to those among the corresponding populations for GARDASIL. At least 99.7% of individuals included in the analyses for each HPV type became seropositive by Month 7.

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating

agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines. The immune response, including the degree of protection from HPV infection, is not yet fully understood in immunocompromised individuals.

1.4 Dose Rationale and Risk/Benefits

The dose and route of administration have been established previously and FDA approved based on the clinical data available to date.

2 Study Objectives

2.1 Primary Outcome

The purpose of this study is to examine levels of HPV antibodies in pre-renal organ transplant and renal transplant recipients who have gotten the HPV vaccine. This knowledge will lead to a better understanding of how effectively the vaccine can help transplant patients get immunity.

The primary outcome is to measure immunogenicity in a patient cohort prior to kidney transplant and in a patient cohort after kidney transplant to each of the nine human papillomavirus types contained in the nanovalent human papillomavirus vaccine (9vHPV) series. We will determine the immune response of this population after the 9vHPV vaccination using the Competitive Luminex Immunoassay (cLIA) testing and Geometric Mean Titers (GMTs) and observe the titers over time. We will be able to compare the immune responses in immunocompromised subjects versus the immune intact population studied previously to obtain FDA approval for HPV vaccinations. Determination of immunogenicity will be based on serum samples collected prior to vaccination, 7 months, 12 months, and 24 months following the first vaccine.

2.2 Secondary Outcome

Secondary analyses will be the utilization of regression analysis to determine the effect of variables on antibody response such as age, gender, race, renal function and type of immunosuppression, and donor type. We will collect data on safety and adverse events 24 and 72 hours after vaccination.

2.3 Exploratory Objectives

Documentation of the rate of seroconversion as well as the rate of seroconversion regression over time may inform best practices recommendations and contribute to evolving Kidney Disease Quality Initiative (KDOQI) vaccination recommendations in this high-risk population.

Follow cohort over the long term and determine whether HPV vaccination impacts subsequent development of HPV-related premalignancy and malignancy in this high-risk population.

Depending on the development of HPV-related morbidity in the study population, we might be able to document antigen concentrations at the time of disease development.

3 Study Design

Group 1	50 patients	Patients prior to renal transplant	9vHPV 0,2,6 months	GMT 0, 7, 12, 24 months
Group 2	50 patients	Patients > 6 months from renal transplant	9vHPV 0,2,6 months	GMT 0, 7, 12, 24 months

4 General Design

This is a prospective cohort open-label nonrandomized single-center observational study. The study duration is anticipated to be 36 months. The expected duration of subject participation is 24 months.

Group 1 (50 patients): Adult patients listed for renal transplant ages 18-45 will be enrolled in the outpatient transplant and nephrology clinic at the Medical College of Wisconsin - Froedtert Memorial Lutheran Hospital.

Group 2: (50 patients): Adult renal transplant recipients ages 18 -45 years > 6 months from transplant will be candidates for participation in the outpatient transplant and nephrology clinics at the Medical College of Wisconsin - Froedtert Memorial Lutheran Hospital.

Patients will be scheduled to receive 3-dose 9vHPV vaccination (vaccination at enrollment [time 0], 2 months [$\pm$ 6 weeks], and 6 months [$\pm$ 6 weeks] per standard guidelines) prior to renal transplantation for one cohort (Group 1) and after renal transplant in the second cohort (Group 2).

Serial serum samples will be obtained for geometric mean titers (GMT) prior to vaccination, at 7 months ($\pm$ 6 weeks), 12 months ($\pm$ 6 weeks), and 24 months ($\pm$ 6 weeks) after completion of the vaccination series. If a patient is subsequently scheduled to undergo a transplant, we will obtain the GMT prior to the transplant.

Subjects will be asked to consent to optional banking of whole-blood for future research and translational studies. Blood will be stored in the Obstetrics & Gynecology Specimen and Data Bank (PRO 11631) at Medical College of Wisconsin.

If subjects chose to participate in the optional banking of their blood, approximately 5 mls of additional blood will be drawn prior to vaccination and at the time of the 7, 12, and 24-month GMT blood draws.

Subjects will be asked if they grant permission for the study team to follow up with them regarding their health status and significant medical history including their association if any with transplant and cancer registries (or other data sources), such as the Scientific Registry of Transplant Recipients in the future.

Anti-HPV antibody responses will be measured using a Competitive Luminex Immunoassay (cLIA) performed by Merck and expressed as geometric mean titers (GMT).

4.1 Primary Study Endpoints

The primary endpoint of the study is to determine the immunogenicity of the 9vHPV vaccination series in pre kidney transplant subjects with chronic kidney disease (GFR < 20 ml/min) and post kidney transplant immunocompromised subjects by drawing serial GMT at specified intervals of 7-, 12- and 24-months post 9vHPV vaccination completion.

4.2 Secondary Study Endpoints

Determination of HPV vaccine prevalence/ uptake in patients pre- and post-renal transplant.

4.3 Primary Safety Endpoints

Safety of the GARDASIL 9 vaccination series in pre kidney transplant subjects with chronic kidney disease (GFR < 20 ml/min) and post kidney transplant immunocompromised subjects.

4.4 Translational Endpoints

We will collect blood samples for patients who are enrolled for additional translational study. we plan to perform immunogenicity profiling on patients pre and post HPV vaccination. We plan to study the subpopulations of immune cells (T and B cells) and attempt to explore the T-cell receptor clonality and repertoire as potential biomarkers.

5 Subject Selection and Withdrawal

5.1 Inclusion Criteria

Both male and female patients between the ages of 18 and 45 years with chronic kidney disease who are on the kidney transplant waiting list and have not received GARDASIL 9.
Both male and female patients between the ages of 18 and 45 years who are at least 6 months post kidney transplant and have not received GARDASIL 9.
Subjects can participate in their health care and sign informed consent.
Subjects may have had bivalent or quadrivalent HPV vaccination previously.
Both living and deceased donor transplant patients are eligible.

5.2 Exclusion Criteria

Contraindication: Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL.
Prior to GARDASIL 9 vaccination completion.
Subjects that are pretransplant and taking immunosuppressive medication.
Subjects listed for or having more than one organ transplant.
Subjects that are planned for kidney re-transplantation.
Subjects with a diagnosis of HIV.
Subjects that endorse being currently pregnant.

5.3 Subject Recruitment and Screening

Patients will be recruited through the investigators and their colleague's clinical practice in the Transplant/ Nephrology clinic at the Medical College of Wisconsin – Froedtert Memorial Lutheran Hospital.

5.4 Early Withdrawal of Subjects

5.4.1 When and How to Withdraw Subjects

Patients that are enrolled prior to transplant (Group 1) but are scheduled to undergo transplant during the vaccination series will not complete the vaccination series per protocol. The remaining doses will not be administered in the first 6 months post-transplant per institutional guidelines. The series can be resumed 6 months post-transplant if agreed upon by treating nephrology/transplant physicians. These subjects will be withdrawn from the study. We will attempt to replace subjects that must be removed from study due to scheduling of transplant.

5.4.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects that are withdrawn from the study will be followed for the standard follow-up period for the study.

6 Study Drug

6.1 Description

GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant Saccharomyces cerevisiae and self-assembled into VLPs. The fermentation process involves growth of S. cerevisiae on chemically defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS).

The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer. GARDASIL 9 is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV Type 6 L1 protein, 40 mcg of HPV Type 11 L1 protein, 60 mcg of HPV Type 16 L1 protein, 40 mcg of HPV Type 18 L1 protein, 20 mcg of HPV Type 31 L1 protein, 20 mcg of HPV Type 33 L1 protein, 20 mcg of HPV Type 45 L1 protein, 20 mcg of HPV Type 52 L1 protein, and 20 mcg of HPV Type 58 L1 protein. Each 0.5-mL dose of the vaccine also contains approximately 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein, and water for injection. The product does not contain preservatives or antibiotics. After thorough agitation, GARDASIL 9 is a white, cloudy liquid.

6.2 Treatment Regimen

GARDASIL 9 should be administered intramuscularly in the deltoid or anterolateral area of the thigh.

- For the 3-dose schedule, GARDASIL 9 should be administered at 0, 2 months, and 6 months.
- For individuals participating in this study, GARDASIL 9 is administered using a 3-dose schedule at 0, 2 months (± 6 weeks), and 6 months (± 6 weeks).

6.3 Method for Assigning Subjects to Treatment Groups

This is a nonrandomized study.

6.4 Preparation and Administration of Study Drug

Method of administration:

- Do not dilute or mix GARDASIL 9 with other vaccines.
- Shake well immediately before use to maintain the suspension of the vaccine.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored. After thorough agitation, GARDASIL 9 is a white cloudy liquid.
- Single-Dose Vial Use Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use it promptly. This package does not contain a needle. Shake well before use. Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe.
- Administer the entire dose as per standard protocol. Administer intramuscularly in the deltoid or anterolateral area of the thigh. Discard the syringe after use.
- Observe patients for 15 minutes after administration. Because individuals that are vaccinated may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes

after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

6.5 Subject Compliance Monitoring

The study team will follow enrolled subjects and call for reminders to subjects to ensure the scheduled doses are administered according to recommended time intervals.

Subjects that are unable to be compliant with the vaccination administration schedule will be withdrawn from participation in the study.

6.6 Prior and Concomitant Therapy

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

Information on concomitant medications will be collected prior to enrollment and at surveillance visits. Subjects will not be permitted to enroll if they have previously completed the GARDASIL vaccination series. Subjects will be allowed to enroll if they previously initiated but did not complete the HPV-9 vaccination series. Subjects will be permitted to participate if they have previously started or completed the Cervarix or quadrivalent HPV (GARDASIL) vaccination series.

6.7 Packaging

GARDASIL 9 is supplied in prefilled syringes. Carton of ten 0.5-mL single-dose vials. NDC 0006-4119-03. Carton of ten 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4121-02

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light. GARDASIL 9 should be administered as soon as possible after being removed from refrigeration. GARDASIL 9 can be administered provided the total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are permitted, as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage 0.5-mL suspension for intramuscular injection as a single-dose vial and prefilled syringe.

Samples can be batched and should be shipped frozen on dry ice (no need to cryofreeze) to the following address:

Q2 Solutions LLC
Attention VACCINES LAB
2400 Ellis Road
Durham, NC 27703

6.8 Blinding of Study Drug

This study is not blinded.

6.9 Receiving, Storage, Dispensing, and Return

6.9.1 Receipt of Drug Supplies

Upon receipt of the study treatment supplies, an inventory must be carried out, and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in each shipment (active drug or comparator) will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit, as well as a packing slip. On delivery of the product to the site, the person in charge of product receipt will check that the cold chain was maintained during shipment (i.e., verification of the temperature recorders). The contents of the shipment will then be reviewed and verified against the packing slip, and will be documented as instructed at the initiation visit. The temperature monitoring device will be read by the responsible person. If the temperature-monitoring device indicates that the cold chain has been broken, the entire shipment must be immediately quarantined in refrigerated conditions (2–8°C)

6.9.2 Storage

All investigational product must be stored in accordance with instructions outlined in the package insert. Investigational product must be stored separately from normal hospital stocks and must be stored in a securely locked area accessible only to authorized trial personnel until dispensed by IDS.

6.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed per IDS to document drug-assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug

reconciliation form or completed within the electronic accountability system, and signed and dated by the study team.

6.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drugs shipped, drugs consumed, and drugs remaining. This reconciliation will be logged on the drug reconciliation form, signed, and dated or completed within the electronic accountability system per IDS. Any discrepancies noted will be investigated, resolved, and documented prior to the return or destruction of the unused study drug. Drugs destroyed on-site will be documented in the study files. Sites may follow their local destruction policy.

7 Study Procedures

The first stage of the study after IRB approval is completed will be to contact patients that are listed for renal transplant to determine interest in participation (Group 1) and patients that are > 6 months from transplantation (Group 2) by phone or during a Transplant Nephrology Clinic visit. Patients interested in participation will sign consent at their subsequent clinic visit if contacted by phone or at the current clinic visit if contacted in person. At the initial clinic visit, they will have the initial serum titer drawn and receive the first GARDASIL 9 vaccine dose.

Participants will be administered dose #2 and dose #3 of the GARDASIL 9 vaccination as per guidelines. These doses will be administered at the MCW (Medical College of Wisconsin) Translational Unit (TRU) or at the Nephrology Transplant Clinic. Serum titers will be drawn at months 7, 12, and 24 after completion of the vaccination series at the TRU or by research nurse draw. The patients will be provided $25 stipends for visits outside of the standard of care visits. Serum titers for the 12 months +/- 6 weeks and 24-month +/- 6 weeks intervals will be drawn. Patients will be asked to document any adverse effects and will be contacted 24 hours and 72 hours post each vaccination.

If a participant agrees to additional optional blood draws for banking in the OB/GYN Specimen and Data Bank (PRO 11631), blood will be drawn at baseline and at 7, 12, and 24 months after completion of the vaccination series.

The study enrollment period would be 24-36 months.

Serial GMTs collected prior to vaccination, at month 7 $\pm$ 6 weeks, month 12 $\pm$ 6 weeks, month 24 $\pm$ 6 weeks. If a listed patient is scheduled to receive a transplant, we would collect the serum GMT prior to the transplant. Specimens will be shipped to Merck for cLIA testing.

7.1 Study Flow Chart

Group 1	50 patients	Patients prior to renal transplant	GARDASIL 9 given at 0,2,6 months	GMT 7, 12, 24 months
Group 2	50 patients	Patients > 6 months from renal transplant	GARDASIL 9 given at 0,2,6 months	GMT 7, 12, 24 months

Trial Period Study Flow Chart	Pre-Screening	Screen	Enrollment	Treatment Period			7 months	12 months	24 months24
Visit Number	1	2[a]	3[a]	4	5	6	8	9	10
Study Day	≤ 14 days	≤ 10 days	1	1	2 mos ± 6 wks	6 mos ± 6 wks	± 6 wks	± 6 wks	± 6 wks
Pre-Screen Phone call	X								
Informed Consent		X							
Inclusion/ exclusion		X							
Demographics		X							
Medical History		X							
Transplant Status		X	X	X	X	X	X	X	X
Physical Exam			X						
GMT blood draw			X				X	X	X
Translational study bank blood draw (optional)			X				X	X	X
GARDASIL 9 Dose				1	2	3			
Phone Call Check **72** hours after vaccination				X	X	X			
Concomitant Medications		X		X	X	X	X	X	X
Adverse Events				X	X	X			

a. Screening and enrollment may occur at same visit

8 Statistical Plan

8.1 Statistical Methods

Statistical methods and sample size justification:
The primary endpoint is to determine seroconversion rates for each HPV type 7 months following first vaccination dose among pre transplant and post-transplant patients. The point estimates and corresponding 95% confidence intervals will be provided for each group.

Sample size is based on obtaining estimates of seroconversion rates at 7 months following the first vaccination dose in each group. Previous studies reported seroconversion rates ranging from 33% to 80% in similar groups of patients. A sample size of about 50 patients in each group would allow us to estimate the seroconversion rates in each group with a 11-14% margin of error with 95% confidence (Table).

Precision of seroconversion estimates for a sample size of 50 patients
P is the hypothesized rate in the population.

Confidence Level	Sample Size (N)	Proportion (P)	Lower Limit	Upper Limit	Margin of Error
0.95	50	30.0%	17.3%	42.7%	12.7%
0.95	50	35.0%	21.8%	48.2%	13.2%
0.95	50	40.0%	26.4%	53.6%	13.6%
0.95	50	45.0%	31.2%	58.8%	13.8%
0.95	50	50.0%	36.1%	63.9%	13.9%
0.95	50	55.0%	41.2%	68.8%	13.8%
0.95	50	60.0%	46.4%	73.6%	13.6%
0.95	50	65.0%	51.8%	78.2%	13.2%
0.95	50	70.0%	57.3%	82.7%	12.7%
0.95	50	75.0%	63.0%	87.0%	12.0%
0.95	50	80.0%	68.9%	91.1%	11.1%

Basic demographic and clinical characteristics will be collected and presented with descriptive statistics.

Chi-square or Fischer's exact test to be used for between group comparisons of categorical variables, and Mann-Whitney U-test to be used for continuous variables.

Logistic regression analysis will be used to evaluate factors influencing seroconversion.

Mixed effect linear regression models will be used to estimate and compare mean titers between groups and within groups over time.

8.2 Subject Population(s) for Analysis

- All-treated population: Any subject randomized into the study that received at least one dose of GARDASIL 9
- Protocol-compliant population: Any subject who was randomized and received the protocol required GARDASIL 9 vaccination series.

9 Safety and Adverse Events

9.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life-threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in an in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

The severity of an event describes the degree of impact and/or the need for medical care necessary to treat an event.

Serious Adverse Events in Clinical Studies
Serious adverse events were collected throughout the entire study period (range one month to 48 months post-last dose) for the seven clinical studies for GARDASIL 9. Out of the 15,705 individuals who were administered GARDASIL 9 and had safety follow-up, 354 reported a serious adverse event: representing 2.3% of the population. As a comparison, of the 7,378 individuals who were administered GARDASIL and had safety follow-up, 185 reported a serious adverse event: representing 2.5% of the population. Four GARDASIL 9 recipients each reported at least one serious adverse event that was determined to be vaccine related. The vaccine-related serious adverse reactions were pyrexia, allergy to vaccine, asthmatic crisis, and headache.

AE grading will be defined by the CTCAE (Common Terminology Criteria for Adverse Events) v5.0. If the CTCAE v5.0 does not apply, the severity descriptions below will be used:

Mild: Asymptomatic, clinical, or diagnostic observations only; intervention not indicated

Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily life

Severe: Medically significant but not immediately life threatening; hospitalization may be required; disabling; limiting activities of daily activity

Life-threatening: Urgent intervention is required.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Relationship to Study Drug
The Investigator is responsible for assessing the relationship to study treatment using clinical judgement and the following considerations:

A. Reporting Procedures for Exchange of Adverse Event Information.

(i) For purposes of this Agreement the below terms shall be defined as follows:

"**Adverse Event**" or "**AE**" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

"**Serious Adverse Event**" or "**SAE**" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious".

"**Suspected Unexpected Serious Adverse Reaction**" or "**SUSAR**" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

(ii) Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction, Potential Incident Reporting: Principal Investigator shall forward to Merck's Global Pharmacovigilance ("Merck GPV") group, any SAE or SUSAR, including, but not limited to, all initial and follow-up information involving any Study subject in the Study. Notification shall be in the form of a completed CIOMS I/MedWatch (or other mutually agreed upon format) within two (2) business days of but not longer than three (3) calendar days of receipt of the information. This information shall be transmitted to Merck GPV using the contact information provided below or such other modified contact information as provided by Merck in writing. All information shall be transmitted in the English language and contain the reporter's name and the Study subject identifier code. SUSAR information will be reported unblinded if the Study Drug has been blinded in the Study. Randomization codes for all other SAEs will be provided to Merck GPV at end of Study if the Study Drug has been blinded in the Study.

(iii) Merck may define certain Non-Serious Events of Interest. If any Non-Serious Events of Interest are defined, Merck will provide such information in writing to Principal Investigator at the time of Protocol approval, execution of this Agreement or anytime thereafter. Reporting of any defined Non-Serious Events of Interest will be handled in the same manner as SAEs unless mutually agreed otherwise in writing by the parties.

(iv) All reports of Study Drug exposure during pregnancy or lactation, whether associated with an AE or not, must be reported to Merck GPV in accordance with the timelines and contact information for an SAE. Principal Investigator shall follow pregnancies to term to obtain the outcome of the pregnancy. The outcome of the pregnancy shall be forwarded to Merck GPV.

(v) Institution and Principal Investigator shall fully comply with all of their respective reporting obligations to the applicable regulatory authorities with respect to any AE, SAE or SUSAR that arises from the Study.

(vi) SAE reports and any other relevant safety information are to be forwarded to Merck GPV facsimile number: 215-661-6229, or toll-free fax 1-800-547-5552. Merck will confirm receipt of the report within one (1) business day. If confirmation is not received within (1) business day, Investigator/Institution will contact Merck to determine if the original report needs to be re-sent. Investigator/Institution will maintain a record of the confirmation.

B. In the event Principal Investigator or Institution becomes aware of a defect or possible defect in the Study Drug provided under this Agreement (or placebo provided by Merck being tested or used as a reference in the Study), Institution and Principal Investigator agree to notify Merck within one business day of first becoming aware of the defect or possible defect.

C. Principal Investigator and Institution further agree to conduct the Study and maintain records and data during and after the term or early termination of this Agreement in compliance with all applicable legal and regulatory requirements, including without limitation, any applicable requirements of the FDA. If required by law, regulation, regulatory authority or to confirm compliance with this Agreement and the Protocol, Merck or Merck's representatives shall have the right to examine and inspect all records and reports related to the Study Drug or directly relating to the Study, at mutually agreeable times with reasonable advance notice and during normal business hours (subject to applicable patient confidentiality considerations). Principal Investigator and Institution agree to take any action necessary, as reasonably requested by Merck, to properly correct or address any deficiencies noted during any inspection and agree to cooperate with Merck with respect to any action taken to address any such deficiencies.

D. Principal Investigator agrees to notify Merck within twenty-four (24) hours in the event that the FDA or any other regulatory authority notifies the Study site of a pending inspection that concerns the Study or Institution’s ability to perform clinical research. In addition, Principal Investigator will forward to Merck any written communication received as a result of the inspection within twenty-four (24) hours of receipt of such communication and agrees to allow Merck to reasonably assist in responding to any citations directly involving the Study Drug. Such responses shall be made as soon as possible under the circumstances or within any earlier deadline set by the issuing regulatory authority. Principal Investigator shall also provide to Merck a complete description of documents and any correspondence provided to any inspector. In the event the FDA or other regulatory authority requests or requires any action to be taken to address any citations, Principal Investigator and Institution agree, after consultation with Merck, to take such action as necessary to address such citations.

E. A copy of all 15 Day Reports and Annual Progress Reports are to be submitted as required by the applicable regulatory authority by the Principal Investigator. Principal Investigator agrees to cross reference this submission according to local regulations, to the Study Drug number (IND, CSA, etc) at the time of submission. Additionally, Principal Investigator agrees to submit a copy of these reports to Merck (Attn: Global Pharmacovigilance; FAX 215-661-6229) at the time of submission to the appropriate regulatory agency.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

All AEs/SAEs occurring after the patient has signed the ICF will be collected and recorded in the AE eCRFs and graded as per CTCAE v4.03. Disease progression is not considered an AE for the purposes of this study.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event and the following condition is met:

- The abnormality is of a degree that the treating physician deems that GARDASIL 9 vaccination is contraindicated

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that is deemed related to GARSDASIL 9 by the clinical investigators and results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition deemed related to GARDASIL 9 by the clinical investigators and responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization is required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in the frequency of hospital admissions as judged by the clinical investigator.

9.2 Recording of Adverse Events

Our study will reside under the oversight of the Medical College of Wisconsin's Institutional Review Board. As such, our research team will be accountable to disclose any adverse experiences related to the study. We will also complete routine continuing progress reports.

Specifically for vaccination-related adverse events, patients will be contacted at 72 hours post-injection to collect adverse event information.

Additionally, biopsy-proven and/ or clinically treated rejection information will be collected up to 6 months from enrollment.

Premalignancy and malignancy information will be collected up to 5 years from enrollment.

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though it should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.3 Reporting of Serious Adverse Events

9.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Denise Uyar, MD
Phone: 414-805-6606
Fax: 414-805-6622

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

9.3.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB within 10 working days. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder.

9.3.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA and Merck by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information. Other serious, unexpected adverse events associated with the use of study drug shall be reported to the FDA no later than 15 calendar days from the sponsors' original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written

report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

9.4 Unblinding Procedures

Not applicable.

9.5 Stopping Rules

The Sponsor reserves the right to temporarily suspend or terminate the study at any time. Reasons for such action taken by the Sponsor include, but are not limited to:

- The discovery of unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision on the part of the Sponsor to suspend, discontinue, or shorten the study

Upon completion of the study, the Investigator will ensure that the complete set of source data has been entered into the eCRFs.

9.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 11 Auditing, Monitoring, and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10 Data Handling and Record-Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of the subject's authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D." If the item is not applicable to the individual case, write "N/A." All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

This study will be monitored by the Sponsor according to the monitoring plan: subjects will be monitored after each injection for 15 minutes per pharmacy protocol and then will be called 72 hours after each injection to confirm tolerability. The investigator will allocate adequate time for such monitoring activities. The HPV9 vaccination is FDA approved and already administered to patients; additional monitoring for tolerance is not part of the standard transplant nephrology care.

The sponsor will review study documents and data at regular intervals. At a minimum, source documentation will be reviewed to substantiate proper informed consent procedures, adherence to protocol procedures, and adequate reporting and follow-up of AEs (Adverse Event).

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliates to the sponsor.

All subjects for this study will be provided with a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment 2 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This study is financed through a grant from Merck Investigator Initiated Studies Program (MISP)

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

13.3 Subject Stipends or Payments

Subjects will receive a $25 gift card for participation in this clinical trial.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. The primary party responsible for the publication of any study results will be Denise Uyar.

15 References

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16 Attachments

i. Informed Consent Form
ii. Instructions for specimen preparation and handling.
iii. Study Flow Chart

Specimen Preparation and Handling Instructions for MERCK GMT analysis:

Note from project manager:
Antibody response to vaccine HPV types is evaluated by a proprietary competitive Luminex immunoassay (cLIA) for vaccine-HPV types and may also be supplemented with the IgG-LIA assay for specific types like 18. Antibodies are reported in Milli Merck Units/mL.

Sample Volume – It is always preferred to have the full 500 microliters; minimum allowed 200 microliters. If less than 200 microliters Q2 may not be able to generate data for both IgG and cLIA.

Sample Aliquoting – It is preferred that samples are sent in screw cap tubes as opposed to snap cap tubes. Samples are then sent to Q2 central lab for aliquoting.

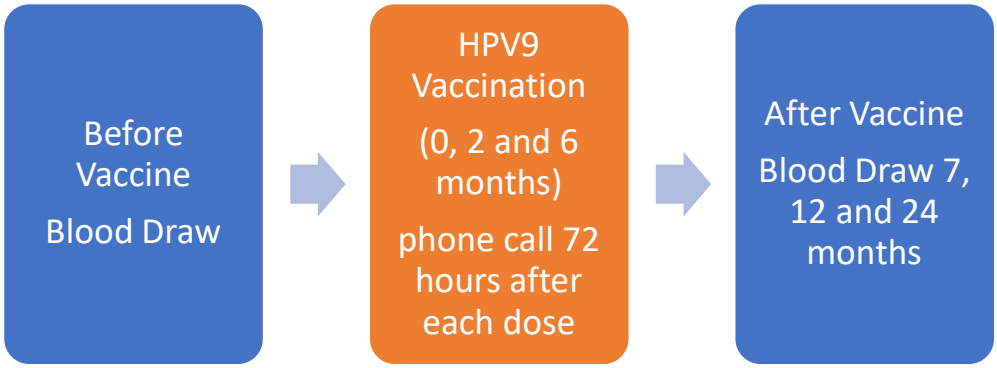
Spread sheet (excel attached) is filled out before samples are shipped.

Samples can be batched and should be shipped frozen on dry ice (no need to cryofreeze) to the following address:

Q2 Solutions LLC
Attention VACCINES LAB
2400 Ellis Road
Durham, NC 27703

Study Flow Chart

Group 1. Subjects listed for renal transplant



Group 2. Subjects > 6 months from completion of transplant