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Study Protocol and Statistical Analysis Plan

Therapeutic intralesional nonavalent HPV vaccine for genital condylomata in adults: an open label pilot study

Protocol Number

NCT05087849

Principal Investigators

- Ayan Kusari, MD

- Kieron S. Leslie, MD

Study Sites

Zuckerberg San Francisco General Hospital

Ward 92 (Building 90, 2nd Floor)

995 Potrero Avenue

San Francisco, CA 94110

1. Background and Rationale

1.1 Background

Genital warts (condyloma) affect 100-200 per 100,000 adults annually. While 90% are caused by HPV types 6 and 11, high-risk HPV types can co-occur and increase dysplasia/carcinoma risk. Current treatments have significant limitations: imiquimod shows variable efficacy (28-56%), while electrocautery, despite high clearance rates (94%), causes discomfort and scarring.

1.2 Preliminary Data

Recent studies demonstrate that intramuscular administration of HPV vaccines (bivalent, quadrivalent, or nonavalent) can promote wart clearance. One study comparing intramuscular to intralesional bivalent HPV vaccine showed superior clearance with intralesional administration (81% vs 63%).

1.3 Rationale

Given the promising results with intralesional bivalent vaccine and the widespread availability of Gardasil 9 in the US, this study aims to assess intralesional Gardasil 9's effectiveness for treating genital condyloma.

2. Study Objectives

2.1 Primary Objective

To assess the efficacy of intralesional Gardasil 9 in treating genital condylomata through:

- Reduction in wart number

- Reduction in mean wart size

- Reduction in total skin area covered by warts

2.2 Secondary Objectives

- Evaluate patient-centered outcomes using:
  - CECA (Specific Questionnaire for Condylomata Acuminata)
  - Dermatology Quality of Life Index (DLQI)
  - Global patient satisfaction (1-5 scale)
- Assess tolerability of intralesional Gardasil 9

3. Study Design

- Prospective, open-label, single-arm proof-of-concept study
- Duration: 12 weeks per participant
- Sample size: 10 participants
- Two treatment visits (Week 0 and Week 4)

4. Study Population

4.1 Inclusion Criteria

- Age ≥ 18 years
- Signed informed consent
- Minimum of 3 genital condylomata, each >3mm in size

4.2 Exclusion Criteria

- Pregnancy or planning pregnancy
- Previous HPV vaccination
- Severe allergies to vaccine components
- Immunosuppressive medications/conditions
- Known HIV infection
- Leukemia or lymphoma

5. Study Procedures

5.1 Visit Schedule

Visit 1 (Week 0)

1. Informed consent
2. Baseline data collection:
   - Demographics
   - Medical history
   - Medication review
   - Condylomata history
3. Pregnancy test if applicable
4. Photography and measurements
5. Questionnaires (CECA, DLQI)
6. Shave biopsy (≤5x5mm) for histologic confirmation
7. First Gardasil 9 injection
8. 15-minute observation period

Phone Follow-up 1 (Week 1)

- Assess adverse effects
- Arrange follow-up if needed

Visit 2 (Week 4)

1. Assessment of treatment response
2. Photography and measurements
3. Questionnaires (CECA, DLQI)
4. Second Gardasil 9 injection if indicated

5. 15-minute observation period

Phone Follow-up 2 (Week 5)

- Assess adverse effects
- Arrange follow-up if needed

Visit 3 (Week 12)

1. Final assessment
2. Photography and measurements
3. Questionnaires (CECA, DLQI, satisfaction)

5.2 Treatment Protocol

- Topical lidocaine 5% pre-treatment
- Total 0.5cc Gardasil 9 distributed across 3-5 index warts
- Intradermal injection immediately subjacent to keratotic wart body

6. Safety Monitoring

6.1 Adverse Event Monitoring

- Weekly phone follow-up after injections
- Documentation of local and systemic reactions
- Access to study clinicians for concerns
- Monthly research team meetings to review safety

6.2 Stopping Criteria

- Intolerable adverse effects
- Worsening of condylomata

- Pregnancy

7. Statistical Analysis Plan

7.1 Sample Size

Pilot study of 10 participants; no formal sample size calculation as effect size is unknown.

7.2 Analysis Populations

- Intent-to-treat (ITT): All participants receiving ≥1 dose
- Per-protocol: Participants completing study without major protocol deviations

7.3 Primary Endpoint Analysis

Paired t-tests comparing baseline to week 12:

- Wart number
- Mean wart size
- Total skin area covered by warts

Significance level: $\alpha = 0.05$

7.4 Secondary Endpoint Analysis

- Paired t-tests comparing baseline to week 12:
  - DLQI scores
  - CECA scores
- Descriptive statistics for:
  - Global satisfaction scores
  - Adverse events
  - Treatment tolerability

7.5 Missing Data

- Last observation carried forward for early discontinuation
- Sensitivity analyses excluding missing data

8. Data Management

8.1 Data Collection

- REDCap electronic data capture
- Standardized photography with measurement software
- Secure storage of identifiable information

8.2 Quality Control

- Monthly data review by PI
- Range checks and validation rules in REDCap
- Regular backup of study data

9. Ethical Considerations

9.1 Risk Mitigation

- Pre-treatment with topical anesthetic
- Close monitoring post-injection
- Direct access to study team
- Emergency equipment available
- ACLS-certified physicians present

9.2 Confidentiality

- Coded study numbers for specimens

- Secure data storage

- Limited access to identifiable information

10. Timeline

- Study Duration: Approximately 6-12 months

- Individual Participation: 12 weeks

- Data Analysis: 3 months post-completion

- Manuscript Preparation: 6 months post-analysis

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Therapeutic intralesional nonavalent HPV vaccine for refractory genital condyloma in adults: an open label pilot study

Research Project Supervisor:	Kieron Leslie, MBBS, Professor of Dermatology UCSF, 1701 Divisadero St, San Francisco, CA 94115. Phone: 415-353-7800; e-mail: Kieron.leslie@ucsf.edu

Principle Investigator and Primary Contact:	Ayan Kusari, M.D., Phone: 628-206-4777 ayan.kusari@ucsf.edu

This is a clinical research study. Your study doctor(s), Ayan Kusari M.D., Eman Bahrani M.D. or Kieron Leslie MBBS from the Department of Dermatology at University of California, San

Francisco and Department of Dermatology at the Zuckerberg San Francisco General Hospital will explain the study to you.

Research studies include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have genital condyloma.

Why is this study being done?

The purpose of this study is to find out what effects injecting Gardasil 9 vaccine (human papillomavirus vaccine) into genital warts has on patients.

How many people will take part in this study?

About 10 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the main part of the study...

You will be asked about your medical history, any medications you are taking, any past allergic reactions that you have had, and if you are capable of pregnancy, then we will ask a few questions about your pregnancy status. There are no laboratory testing or procedures that will be performed as part of the initial screening process.

During the main part of the study...

You will take part in three visits spaced out over three months. At the first visit, you will fill out a questionnaire, we will count and measure all of your genital warts, and de-identified photos of your warts will be taken, your skin will be numbed first with the cream and then with an injection. Then a small sample of your skin will be taken using a curved blade and sent for laboratory analysis. Then, we will inject up to 5 of your warts with the vaccine. the thought is that this injection may be able to stimulate your immune system to fight the wart. this visit should take about 2 hours.

One month later, you will return to our study site for a re-evaluation. We will ask you some questions, ask you to fill out a few more questionnaires, take comparison photos and determine if you have any warts left. If you have any warts left, then we will inject the warts again with the Gardasil 9 vaccine to try and stimulate an immune response. This visit should take between 30 and 90 minutes. This will be the last time you receive injection of the wart with Gardasil 9 as part of this study.

When you are finished receiving Gardasil 9…

Two months after the second visit, you will return to our site for a re-evaluation. We will again ask you some questions, have you fill out questionnaires, take more photos and determine if there is any wart left. This visit should take about 30 minutes. At this visit we will do a wrap-up and debrief about your experiences in study, and arrange post follow up in our general dermatology clinic for standard care for genital warts.

- **Study location:** All study procedures will be done at Zuckerberg San Francisco General Hospital, Building 90, Second floor (Ward 92 Dermatology)

Summary of study events

Visit number	Timeline	Main procedure	Other activities	Time commitment
Visit 1	--	Gardasil injection #1	photos, surveys	2 hours
Visit 2	1 month after visit 1	Gardasil injection #2	photos, surveys	30-90 min
Visit 3	2 months after visit 2	Re-check	photos, surveys, debrief	30 min

- **How long will I be in the study?**

You will be asked to take Gardasil 9 on up to two occasions spaced one month apart. After you are finished receiving the Gardasil 9 vaccine , the study doctor will ask you to visit the office for one further follow-up exam two months after the second visit. if your genital warts have not completely resolved by the end of the study, we will be sure to arrange routine follow up in our regular clinic so we may continue to work on the problem.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from Gardasil 9 vaccine can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

There are two main categories of risk to think about when deciding to participate in the study. The first set of risks is related to injection of the Gardasil 9 vaccine. The second set of risks is related to the biopsy that will do as a part of the study.

<u>Risks related to injection of Gardasil 9:</u>

- You might experience pain with the injection; you will be offered a numbing cream beforehand at no charge to make the experience more comfortable.
- The injection is a vaccine, and vaccines wake up the immune system, which is normally responsible for fighting infections (including warts). The vaccine might cause local redness and swelling as your immune system attacks the wart. If this is too much, you can let us know, and we can provide you with a steroid cream that will slow down the immune response.
- Sometimes, vaccines can activate the immune system so much that you get fevers, chills and/or nausea, and there is a theoretical risk that you may experience this with the Gardasil 9 vaccine. However, is very rare with Gardasil 9 vaccine, especially compared to many other vaccines.
- Needles can be scary, and many people feel light-headed or faint when they are around needles. If this has happened to you before please let us know before we proceed and we can take appropriate precautions. no matter what, we will recommend that you stay in the room for 15 minutes after each injection so we can observe you and make sure you aren't feeling bad.
- Warts themselves often leave behind a dark or light smudge or a scar on the skin even after the wart virus has gone away. whenever a wart treatment act by activating the immune system, that may theoretically lead to a larger area of color change or (in very rare cases), a larger scar, because there is more inflammation. The dark or light smudge will resolve with time; scars may improve with time but usually do not go away completely.

Risks related to biopsy:

- A biopsy is a sample of the skin taken with a small, curved handheld blade. We will be using this biopsy to confirm that the spot we are treating is truly a wart, and to test which species of wart virus (human papillomavirus) is responsible.
- In general, taking a skin sample can be associated with discomfort, bleeding and scar formation, and these are all possible with the shave biopsy that will be performed as a part of this study.
- The risks of all three are low given the small and superficial nature of the biopsy that will be done. We will also be providing the numbing cream that will further help reduce discomfort.
- If you feel any discomfort with the biopsy process, please let the study clinician know and they can give you more numbing medication.

- **Reproductive risks:** The vaccine Gardasil 9 in this study might potentially affect an unborn baby or infant. You should not become pregnant while on this study. If you can become pregnant, you must have a pregnancy test before you enter this study and at regular intervals during the study. If applicable to your situation, you must use contraception the entire time you are in the study. Acceptable methods of contraception are:
    - An intrauterine device (IUD)
    - Hormone-based contraceptives (birth control pills)
    - Condoms (male or female) must be used with another method, other than spermicide.
    - Complete abstinence from sexual activity that could result in pregnancy.

  If you think you may be pregnant at any time during the study, tell the study staff right away.

- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

- For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope this treatment will be more useful against genital warts compared to the usual treatment, there is no direct proof of this. We do know that the information from this study will help doctors learn

more about Gardasil 9 a treatment for genital warts. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your warts without being in a study.
- Taking part in another study
- Getting no treatment

Please talk to your doctor about your choices before deciding if you will take part in this study.

How will my specimens and information be used?

Researchers will use your specimens and information to conduct this study. Once the study is done using your specimens and information, we may share them with other researchers so they can use them for other studies in the future. We will not share your name or any other personal information that would let the researchers know who you are. We will not ask you for additional permission to share this de-identified information.

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Are there any costs to me for taking part in this study?

No. The sponsor has agreed to pay for all items associated with this research study; you or your insurer will not be billed.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctors, Ayan Kusari M.D., Eman Bahrani M.D. and Kieron Leslie M.D. if you feel that you have been injured because of taking part in this study. You can tell any of the study doctors in person or call them at 628-206-4777.

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California or the study sponsor *[sponsor name]*, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Institutional Review Board at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) Ayan Kusari M.D., Eman Bahrani M.D. and Kieron Leslie M.D. at 628-206-4777.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the office of the Institutional Review Board at 415-476-1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At

most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent