

## Protocol Synopsis

### Title

A randomized, placebo-controlled, phase IIIb HPV vaccination trial with Gardasil® in patients with recurrent condylomata acuminata.

### Short Title

GaReCo

### Phase

IIIb

### Sponsor

DKFZ, Im Neuenheimer Feld 280, 69120 Heidelberg

### Coordinating Investigator (LKP)

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### Financing/ Status of the Sponsor

DKFZ, Im Neuenheimer Feld 280, 69120 Heidelberg / non-commercial

### Indication

Condylomata acuminata (at least one lesion) defined as:

- Condylomata acuminata
- Condylomata gigantea
- Keratotic genital warts
- Papular warty-like lesions

### Study Population

Patients with recurrent external condylomata acuminata located at the following genital regions: labia minora and majora, introitus vaginae, clitoris, prepuce, glans penis, coronal sulcus and frenulum, perianal skin, perineal region, inguinal- and pubes region.

The following anogenital regions are excluded: urethra, anal canal and vagina.

Patients who have internal condylomata acuminata in addition to the external condylomata acuminata are also eligible.

### Inclusion/Exclusion Criteria

#### Inclusion Criteria

- External condylomata acuminata (at least one) defined as: condylomata acuminata, condylomata gigantea, keratotic genital warts, papular warty-like lesions within 6 months after removal of previously clinically diagnosed external condylomata acuminata (at least one)

- Willingness for single session ablation by scissor snip excision, curettage, electrocautery or laser surgery
- Age  $\geq$  18
- Ability of patient to understand character and individual consequences of the clinical trial
- Provision of written informed consent

#### Exclusion Criteria

- Contraindications to vaccination with Gardasil® according to the summary of product characteristics
- HIV infection or other known immune deficiency disease or current treatment with immunosuppressive drugs
- Syphilis (clinical features of first stage and second stage)
- Previous treatment with Imiquimod within the last 30 days prior to visit 1
- Previous/concomittant treatment with any other immunomodulators within the last 90 days prior to visit 1
- Previous immunization with Gardasil® or Cervarix
- Patients who are unlikely to adhere to the protocol
- Participation in other ongoing clinical trials or during their observation period
- Pregnancy (women of child bearing potential, WOCBP, will be asked before enrollment and at visit 4, and a pregnancy urine test will be performed at visits 1 - 3 before study medication is applied)

#### Objectives

##### Primary Objective

To evaluate the efficacy of Gardasil® compared with placebo on the prevention of recurrence of condylomata acuminata.

##### Secondary Objective(s)

To compare Gardasil® versus placebo with respect to:

- Time to recurrence of condylomata acuminata from the day of administration of first vaccination up to 6 months after last vaccination
- Incidence of HPV 6/11 related external condylomata acuminata
- Presence (DNA) and biological activity (RNA) of HPV6/11 and other HPV types in condylomata acuminata at visit 1 to visit 4
- HPV specific immunological outcomes (HPV antibody at visit 1 to visit 4 and T-cell responses at visit 1, visit 3 and visit 4)
- Associations between immunological and clinical outcomes
- Safety and tolerability

#### Study Design

Phase IIIb, randomized, placebo-controlled, multicenter, parallel, two-arm study. Upon meeting eligibility criteria, patients will be randomized (1:1) to one of the two following treatment arms: Gardasil® or placebo. Patients, who were randomized in the placebo group, will be offered to receive Gardasil® at their last study visit (visit 4, month 12) outside the trial protocol.

#### Investigational Medicinal Product

Gardasil® (vaccination according to schedule: month 0, 2, 6)

**Number of patients:** 200

**Planned Number of Participating Sites:** 7 sites in Germany

### **Trial Duration and Dates**

|                                  |   |
|----------------------------------|---|
| Total trial duration:            | 48 months                                     |
| Duration of the clinical period: | 36 months (including 2 years for recruitment) |
| FPI (First patient in):          | 29 April 2014                                 |
| LPI (Last patient in):           | Q1 2016                                       |
| LPO (Last patient out):          | Q1 2017                                       |
| Trial Report completed:          | Q1 2018                                       |

### **Sample Size**

The sample size calculation is based on comparison of the proportion of recurrence in the two treatment groups using the following main assumptions: Equal group sizes, group difference of 25% in the recurrence rates, two-sided Chi<sup>2</sup> test with 5% significance level. Under the above assumptions a sample size of 85 in each group will provide 90% power to detect a treatment difference from 50% on placebo to 25% on Gardasil®. Assuming, that about 15% of the patients randomized to the trial will drop-out, a total of 100 patients per treatment arm is needed.

### **Statistical Analysis**

#### **Analyses Sets**

The Full Analysis Set (FAS) includes all randomized patients and will be used for the primary analysis. The Per Protocol Set (PPS) includes all patients from the FAS without any major protocol deviation, and who are evaluable for efficacy. The PPS will be used for secondary analyses of efficacy. The safety population includes all patients who have received at least one dose of study treatment.

#### **Primary Analysis**

The primary analysis will be a comparison of the recurrence rates in the two arms using a two-sided Cochran-Mantel-Haenszel (CMH) test adjusted for site effects. Summary tables will present the number of patients observed with recurrence, the corresponding percentages and exact 95% CIs.

#### **Secondary Analyses**

- A sensitivity analysis will be performed on the primary efficacy variable to assess the impact of protocol deviations using the per protocol analysis set.
- Benefit from the intervention (recurrence yes /no) will be explored using a logistic regression model. The model will include terms for treatment, study site and relevant prognostic factors as covariates.
- For the time to recurrence, the event rates will be derived from the Kaplan Meier estimate and the confidence intervals will be calculated using Greenwood's formula.
- All other secondary variables will be analyzed using descriptive and explorative methods.
- Adverse Events (AE) will be coded with the MedDRA dictionary. Summary tables will present the number of patients observed with AEs, the corresponding percentages, and exact 95% CIs.
- Patient disposition will be tabulated. The number of patients who withdrew from the study and reasons for discontinuation will be summarized. Baseline characteristics, concomitant

medications, study drug administration and reasons for the deviations from the planned therapy will be tabulated. Summary tables will be prepared to examine the distribution of laboratory measures over time.

No interim analyses are planned.

## Study Schedule

| Visit   | Screening <sup>1</sup>   | Visit 1        | Visit 2               | Visit 3               | Visit 4                |
|---|--------------------------|----------------|-----------------------|-----------------------|------------------------|
| Month   | -14 to 0 days to Visit 1 | Month 0        | Month 2 (+/- 4 weeks) | Month 6 (+/- 8 weeks) | Month 12 (+/- 4 weeks) |
| Informed Consent  | x                        |                |                       |                       |                        |
| In-/Exclusion Criteria  | x                        |                |                       |                       |                        |
| Physical Examination  |                          | x              | x                     | x                     | x                      |
| Pregnancy urine test (WOCBP)  |                          | x              | x                     | x                     |                        |
| Medical History   | x                        |                |                       |                       |                        |
| Randomization   | x                        |                |                       |                       |                        |
| Swab test (HPV DNA/RNA; central lab DKFZ)   |                          | x              | x                     | x                     | x                      |
| Biopsy (5mm punch or scissors excision to investigate histology and molecular marker) |                          | x              | (x) <sup>2</sup>      | (x) <sup>2</sup>      | (x) <sup>2</sup>       |
| Blood sample (2 ml) <sup>3</sup>  |                          | x              | x                     | x                     | x                      |
| Blood sample (20 ml full blood) <sup>4</sup>  |                          | x              |                       | x                     | x                      |
| Vaccination (Gardasil® /Placebo)  |                          | x              | x                     | x                     | (x) <sup>5</sup>       |
| Adverse Event   |                          | x <sup>6</sup> | x <sup>6</sup>        | x <sup>6</sup>        | x                      |
| Pre- and concomitant medications  | x                        | x              | x                     | x                     | x                      |

<sup>1</sup> It is possible to perform the Screening Visit at the same day as Visit 1.

<sup>2</sup> Biopsy will be repeated in case of recurrence before ablation of recurrent condylomata acuminata.

<sup>3</sup> The blood sample will be analyzed at the DKFZ

<sup>4</sup> If patient has agreed in the informed consent for additional blood sampling there will be an additional blood sample at visit 1, visit 3 and visit 4 to assess HPV T cell immunity.

<sup>5</sup> Patients of the placebo group will be offered to receive Gardasil® vaccination outside the trial protocol

<sup>6</sup> Assessment of Adverse Events during vaccination will be documented by the applier of the vaccination

## Flow Chart

|  |  |  |
|--|--|--|
| Screening  | Informed Consent<br>Assessment of Eligibility Criteria<br>Check prior medication<br>Physical Examination<br>Medical History<br>Negative Pregnancy status (ask for information)   |  |
|  | Randomization (Gardasil® or Placebo)   |  |
| Visit 1<br>Month 0<br>(can be done directly after screening) | Pregnancy urine test (WOCBP)<br>Swab test<br>Biopsy<br>Blood sample (serum)<br>Blood sample (full blood) <sup>2</sup><br>Vaccination (Gardasil®)<br>Adverse Event<br>Concomitant Medication                                      | Pregnancy urine test (WOCBP)<br>Swab test<br>Biopsy<br>Blood sample (serum)<br>Blood sample (full blood) <sup>2</sup><br>Vaccination (Placebo)<br>Adverse Event<br>Concomitant Medication                                      |
| Visit 2<br>Month 2   | Pregnancy urine test (WOCBP)<br>Physical Examination<br>Swab test<br>Biopsy <sup>1</sup><br>Blood sample (serum)<br>Vaccination (Gardasil®)<br>Adverse Event<br>Concomitant Medication   | Pregnancy urine test (WOCBP)<br>Physical Examination<br>Swab test<br>Biopsy <sup>1</sup><br>Blood sample (serum)<br>Vaccination (Placebo)<br>Adverse Event<br>Concomitant Medication   |
| Visit 3<br>Month 6   | Pregnancy urine test (WOCBP)<br>Physical Examination<br>Swab test<br>Biopsy <sup>1</sup><br>Blood sample (serum)<br>Blood sample (full blood) <sup>2</sup><br>Vaccination (Gardasil®)<br>Adverse Event<br>Concomitant Medication | Pregnancy urine test (WOCBP)<br>Physical Examination<br>Swab test<br>Biopsy <sup>1</sup><br>Blood sample (serum)<br>Blood sample (full blood) <sup>2</sup><br>Vaccination (Placebo)<br>Adverse Event<br>Concomitant Medication |
| Visit 4<br>Month 12  | Physical Examination<br>Swab test<br>Biopsy <sup>1</sup><br>Blood sample (serum)<br>Blood sample (full blood) <sup>2</sup><br>Adverse Event<br>Concomitant Medication  | Physical Examination<br>Swab test<br>Biopsy <sup>1</sup><br>Blood sample (serum)<br>Blood sample (full blood) <sup>2</sup><br>Adverse Event<br>Concomitant Medication  |

<sup>1</sup>Biopsy will be repeated in case of recurrence

<sup>2</sup>With informed consent for T cell immunity