Clinical Trial Protocol

A randomized, placebo-controlled, phase IIIb HPV vaccination trial with Gardasil® in patients with recurrent condylomata acuminata (GaReCo-Study)

Clinical Trial Code:	NCT-2010-1090
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Summary

Infection with certain types of human papillomavirus (HPV), most frequently HPV 6 and 11, cause genital warts (condylomata acuminata). Although different methods for treatment of condylomata acuminata are applied there is a high rate of failure. It has been shown that the HPV vaccine Gardasil® is active against HPV types 6 and 11 and prevents condylomata acuminata in HPV-naive males and females. This randomized, placebo-controlled, multicenter, national, phase IIIb study will examine the hypothesis that Gardasil® vaccination might prevent recurrence of condylomata acuminata caused by HPV type 6 or 11.

Male and female patients with recurrent condylomata acuminata participating in this study will, in addition to the ablative therapy (standard of care), receive vaccination with either Gardasil® or placebo (NaCl solution) at month 0, 2, and 6. They will be followed for 6 months and will provide a blood sample and a swab of the treated and the contralateral region at each visit (month 0, 2, 6, 12). A biopsy will be performed prior to ablation. Endpoint of the trial is recurrence of condylomata acuminata within 6 month after the third vaccination. Thus, this trial will provide knowledge concerning the efficacy of Gardasil® vaccination in prevention of recurrent condylomata acuminata.

Zusammenfassung

Infektion mit bestimmten Typen humanpathogener Papillomviren (HPV) führt zur Entstehung von Genitalwarzen (Condylomata acuminata). Obwohl für die Behandlung von Condylomata acuminata verschiedene Methoden angewandt werden, ist die Rezidivrate hoch. Es konnte gezeigt werden, dass der HPV-Impfstoff Gardasil® gegen die Infektion mit den HPV-Typen 6 und 11 schützt und Condylomata acuminata bei HPV-naiven Frauen und Männern verhindert. In dieser randomisierten, placebokontrollierten, multizentrischen, nationalen Phase IIIb Studie wird untersucht, ob die Impfung mit Gardasil® auch das Wiederauftreten von Condylomata acuminata, verursacht durch die HPV Typen 6 und 11, nach Standardtherapie verhindert.

An dieser Studie nehmen Patienten und Patientinnen mit rezidivierenden Condylomata acuminata teil, die zusätzlich zur ablativen Therapie (Therapiestandard) im Monat 0, 2, und 6 eine Impfung mit Gardasil® oder Placebo (NaCl-Lösung) erhalten. Sie werden bis 6 Monate nach der dritten Impfung beobachtet. Von den Patienten wird bei jedem Besuch (Monat 0, 2, 6, 12) eine Blutprobe und je ein Abstrich an der behandelten und der kontralateralen Seite entnommen. Eine Gewebeprobe wird vor der Ablation entnommen. Endpunkt der Studie ist das Wiederauftreten von Condylomata acuminata innerhalb von 6 Monaten nach der dritten Impfung.

Diese Studie wird Erkenntnisse über die Wirksamkeit von Gardasil® in der Rezidivprophylaxe von Condylomata acuminata liefern.

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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

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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 3 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 ≥ 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 immunomodulators (i.e. Imiquimod) within the last 30 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 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: 6 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):	Q2 2013
LPI (Last patient in):	Q2 2015
LPO (Last patient out):	Q2 2016
Trial Report completed:	Q2 2017

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^2 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[1]	Visit 1	Visit 2	Visit 3	Visit 4
Month	-7 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)[2]	(x)[2]	(x)[2]
Blood sample (2 ml)[3]		x	x	x	x
Blood sample (20 ml full blood)[4]		x			x
Vaccination (Gardasil® /Placebo)		x	x	x	(x)[5]
Adverse Event		x[6]	x[6]	x[6]	x
Pre- and concomitant medications	x	x	x	x	x

[1] It is possible to perform the Screening Visit at the same day as Visit 1.

[2] Biopsy will be repeated in case of recurrence before ablation of recurrent condylomata acuminata.

[3] The blood sample will be analyzed at the DKFZ

[4] If patient has agreed in the informed consent for additional blood sampling there will be an additional blood sample at visit 1 and visit 4 to assess HPV T cell immunity.

[5] Patients of the placebo group will be offered to receive Gardasil® vaccination outside the trial protocol

[6] Assessment of Adverse Events during vaccination will be documented by the applier of the vaccination

Flow Chart

Screening/ Visit 1 Month 0	Informed Consent Assessment of Eligibility Criteria Check prior medication Physical Examination Medical History Negative Pregnancy status (ask for information)	
Visit 1 Month 0	Pregnancy urine test (WOCBP) Swab test Biopsy Blood sample (serum) Blood sample (full blood)[2]	Pregnancy urine test (WOCBP) Swab test Biopsy Blood sample (serum) Blood sample (full blood)[2]
	Randomization (Gardasil® or Placebo)	
	Vaccination (Gardasil®) Adverse Event Concomitant Medication	Vaccination (Placebo) Adverse Event Concomitant Medication
Visit 2 Month 2	Pregnancy urine test (WOCBP) Physical Examination Swab test Biopsy[1] Blood sample (serum) Vaccination (Gardasil®) Adverse Event Concomitant Medication	Pregnancy urine test (WOCBP) Physical Examination Swab test Biopsy[1] Blood sample (serum) Vaccination (Placebo) Adverse Event Concomitant Medication
Visit 3 Month 6	Pregnancy urine test (WOCBP) Physical Examination Swab test Biopsy[1] Blood sample (serum) Vaccination (Gardasil®) Adverse Event Concomitant Medication	Pregnancy urine test (WOCBP) Physical Examination Swab test Biopsy[1] Blood sample (serum) Vaccination (Placebo) Adverse Event Concomitant Medication
Visit 4 Month 12	Physical Examination Swab test Biopsy[1] Blood sample (serum) Blood sample (full blood)[2] Adverse Event Concomitant Medication	Physical Examination Swab test Biopsy[1] Blood sample (serum) Blood sample (full blood)[2] Adverse Event Concomitant Medication

[1]Biopsy will be repeated in case of recurrence
[2] With informed consent for T cell immunity

Abbreviations

AE	Adverse Event
ATC	Anatomisch Therapeutisch Chemisches Klassifikationssystem
AMG	German Drug Law (Deutsches Arzneimittelgesetz)
BDSG	Bundesdatenschutzgesetz
CI	Confidence Interval
CI	Coordinating Investigator (LKP)
CRF	Case Report Form
DKFZ	Deutsches Krebsforschungszentrum
DSUR	Development Safety Update Report
EC	Ethics Committee
FAS	Full Analysis Set
FFPE	Formalin-fixed and Paraffin-embedded
FPI	First Patient In
GCP	Good Clinical Practice
GCP-V	Good Clinical Practice Ordinance (GCP-Verordnung)
IB	Investigator´s Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
ISF	Investigator Site File
KKS	Coordination Center for Clinical Trials (Koordinierungszentrum für klinische Studien)
LDSG	Landesdatenschutzgesetz
LKP	Coordinating Investigator according to AMG (Leiter der Klinischen Prüfung)
LPI	Last Patient In
LPO	Last Patient Out
NA	Not applicable
NCT	Nationales Centrum für Tumorerkrankungen
PEI	Paul-Ehrlich-Institut
PPS	Per Protocol Set
SAE	Serious Adverse Event
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TMF	Trial Master File
TRP	Trial-related Procedures
WOCBP	Women Of Child Bearing Potential

1 Introduction

1.1 Scientific Background and Trial Rationale

Human papillomavirus (HPV) comprise a heterogeneous group of infectious agents ("HPV types") that infect epithelia of the skin and mucosae. Depending on the site of infection and the HPV type involved infections either remain clinically inconspicuous, lead to benign exophytic epithelial proliferations (warts, papillomas) or induce intraepithelial lesions at the genital mucosa that, under rare circumstances, can progress into so-called high-grade lesions and ultimately malignant anogenital tumors such as cancer of the uterine cervix. According to their oncogenic potential papillomaviruses that are infecting the genital tract are being separated into low-risk (LR) and high-risk (HR) HPV types (reviewed in Munoz et al., 2006).

One of the hallmarks of human papillomaviruses is their ability to establish persistent infections. This is particular well documented in case of the HR types where persistent infection appears to be a precondition for development of malignancies (reviewed in Kjaer et al., 2002). The current model of persistence involves the infection of a certain set of basal cells within the epithelium (possibly epithelial stem cells) where the viral DNA establishes itself in a few hundred copies per cell and remains there in a latent state even after separation of daughter cells that initiate their program of differentiation which involves the support of virus DNA replication, expression of viral proteins and ultimately production of virus progeny. This low-level virus replication typically remains without cytologic and morphologic signs of infection (Maglennon et al., 2011). There is evidence that cellular immunity against early viral proteins (E6, E7, E2) that are required for maintaining the persistence of the DNA may be able to eliminate infected stem cells and thus terminate a persistent infection (Maglennon et al., 2011).

Warts in the anogenital tract (called genital warts or condylomata acuminata) are caused by HPV types 6 or 11 in >90% of cases. Due to changing sexual behavior the incidence of genital warts has been dramatically increased since the last 40 years. In Germany, the incidence of condylomata acuminata was described as 171 per 100.000 for new cases in women aged 14-25 years and 53 per 100.000 for recurrent cases in women aged 26-45 (Hillemanns et al, 2008). Numbers from males do not exist for Germany but, according to experience in other countries, they are expected to be of similar magnitude. Treatment of condylomata acuminata includes surgery, electrocautery, laser surgery and caustic chemicals (Beutner and Ferenczy, 1997). However, treatment failure is high, varying from 30-70% (Pelisse and Barasso, 2003). Compared to HR HPV types HPV 6 and 11 show a much higher yield of virus production and a lesser risk of persistence hence we hypothesize that the basis for recurrent genital warts is not the activation of latently infected basal cells but rather the reinfection of basal cells within the same area either by auto-inoculation or from a sexual partner (Grussendorf-Conen et al., 1983).

Gardasil® is a licensed HPV vaccine (manufactured by Merck, Sharpe & Dome and distributed in Europe by Sanofi-Pasteur MSD) consisting of “virus-like particles“ (VLP) of HPV types 6, 11, 16 and 18 that form spontaneously in the presence of high concentration of the L1 major structural proteins. It is produced in yeast following a standardized biotechnological process that ensures a high safety profile as it was demonstrated in clinical studies and in post-licensure surveillance.

In clinical studies Gardasil® proved to prevent incident and persistent HPV 6 and 11 HPV infections within the genital tract of both males and females and the development of genital warts (Villa et al, 2005; Reisinger et al., 2007; Giuliano et al., 2011). Moreover, after introduction of Gardasil® in Australia in 2007 for girls (12-13 years with a catch-up between 12 and 25 years) reaching >80% coverage, the incidence of genital warts dropped to about 10% within 4 years in women up to 29 years. Interestingly, a reduction was recorded also in heterosexual men (who are not included in the vaccine program) due to herd immunity. No effect was seen in men who have sex with men (MSM), in women >30 years of age and in non-residents (Read et al., 2011). It is generally accepted that protection is conferred by neutralizing antibodies, yet the protective titer and the relevance of antibodies specific for particular viral epitopes are unknown. The clinical studies have also clearly demonstrated that Gardasil® has no therapeutic effect, i.e.

vaccinated individuals with an existing HPV 6 or 11 infection at enrollment have a similar risk of developing genital warts within the next 18 months as the placebo recipients (Garland et al., 2007).

According to our hypothesis recurrent condylomata acuminata will be prevented by induction of neutralizing antibodies thus one could achieve a "therapeutic effect" with a prophylactic vaccine. In fact, such results have already been obtained in a non-placebo-controlled study of 33 patients with recurrent genital warts. After surgery they received a non-licensed HPV 6 vaccine without adjuvant. Twenty five of the patients presented with a disease-free interval of 6 months, a highly significant effect compared to historic controls (Zhang et al., 2000). Several anecdotal results have also been published about successful treatment of laryngeal papillomas with a post-surgery immunization with Gardasil® that are also caused by infection with HPV 6 or 11 and show a similar biology as genital warts (reviewed in Pawlita and Gissmann, 2009).

1.2 Benefit/ Risk Assessment

Prevention of recurrent condylomata acuminata represents a significant unmet medical need. It is presumed that Gardasil® vaccination might prevent re-infection with HPV 6 and 11 resulting in reduced recurrence of condylomata acuminata. The prospective benefit for all patients will be to gain knowledge concerning efficacy of Gardasil® vaccination in reducing incidence of condylomata acuminata and their recurrence.

As shown in the study schedule the study related procedures include (a) biopsy of the lesion(s) (b) swab(s) (c) blood sampling and (d) triple injection of Gardasil® or NaCl solution. Other Gardasil® vaccination studies have shown no risks related to the vaccination other than local and systemic side effects typical for vaccinations. With informed consent of the patient there will be an extra blood sample at visit 1 and visit 4 to assess T cell immunity.

2 Trial Objectives and Endpoints

2.1 Primary Objective and Primary Endpoint

Primary objective is to evaluate the efficacy of Gardasil® compared with placebo on the prevention of recurrence of condylomata acuminata.

The primary endpoint is the recurrence rate of condylomata acuminata within 6 month after the third vaccination. Recurrence is defined as (1) the presence of new lesion(s) in the area which had been treated or (2) appearance of new warts on other genital sites. All recurrences are verified by biopsy and histology.

2.2 Secondary Objectives

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 and visit 4)
- Associations between immunological and clinical outcomes
- Safety and tolerability

3 Trial Design

This is a randomized, placebo-controlled, parallel, two-arm, multicenter, national, phase IIIb study to evaluate the efficacy, safety and tolerability of Gardasil® vaccination as compared with placebo.

Patients, who qualify will be randomized at visit 1 to receive either Gardasil® or placebo (randomization ratio 1:1).

Patients with recurrent condylomata acuminata who are treated at one of the participating sites will be included in this trial. All patients will be informed about possible trial participation in addition to their usual treatment. Prior to condyloma ablation a swab of the lesion and an additional swab of a non-lesion surface will be taken. A biopsy will be taken and will be examined histological. Patients of the verum group will be vaccinated with Gardasil® according to the schedule of the Summary of Product Characteristics (SPC) (month 0, 2, 6). Patients of the placebo group will receive a NaCl injection instead. All patients will provide a blood sample at month 0, 2, 6 and 12 to determine HPV serology. An additional blood sample will be taken from patients who agreed in the informed consent for analysis of T cell immunity at visits 1 and 4, respectively. Swabs will be taken at every visit (month 0, 2, 6, 12). Patients, who were randomized in the placebo group, will be offered to receive Gardasil® at visit 4 outside the trial protocol.

4 Trial Duration and Schedule

The duration of the clinical period for each patient is expected to be 12 months including 6 months of follow-up. The overall duration of the clinical period is expected to be approximately 36 months including 2 years for recruitment. Recruitment of patients is planned to start in Q2 2013. The actual overall duration or recruitment may vary.

The end of the clinical study is defined as the end of the clinical period when the last patient has its last visit. The trial report will be written after the end of the clinical period.

Total trial duration:	48 months
Duration of the clinical period:	36 months (including 2 years for recruitment)
FPI (First Patient In):	Q2 2013
LPI (Last Patient In):	Q2 2015
LPO (Last Patient Out):	Q2 2016
Trial Report completed:	Q2 2017

5 Selection of Patients

5.1 Number of Patients

As calculated in section 10.2 Sample Size Calculation, 200 patients should be included in the clinical trial, i.e. 100 patients per treatment group at approximately 6 study sites. It is estimated that at least 400 patients should be screened to achieve the required number of evaluable patients with an anticipated screen failure rate of approximately 50%.

5.2 General Criteria for Patients' Selection

Patients with recurrent external condylomata acuminata are eligible to participate in this trial.

External condylomata acuminata (at least one lesion) are defined as:

- Condylomata acuminata

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

located at the following genital regions: labia minora and majora, introitus vaginae, clitoris, prepuce, glans penis, coronal sulcus, 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.

5.3 Inclusion Criteria

Patients meeting all of the following criteria will be considered for admission to the trial:

- External condylomata acuminata (at least one) defined as: condylomata acuminata, condylomata gigantea, keratotic genital warts, papular warty-like lesions within 3 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 ≥ 18
- Ability of patient to understand character and individual consequences of the clinical trial

Provision of written informed consent

5.4 Exclusion Criteria

Patients presenting with any of the following criteria will not be included in the trial:

- 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 immunomodulators (i.e. Imiquimod) within the last 30 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 (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)

No patient will be allowed to enrol in this trial more than once.

5.5 Criteria for Withdrawal

5.5.1 Withdrawal of Patients from further trial-related procedures (TRP)

A patient will/may be withdrawn from further TRP for the following reasons:

- At any time at his/her own request
- If, in the investigator's opinion, continuation of TRP would be detrimental to the patient's well-being

- Occurrence or ex-post detection of exclusion criteria
- Occurrence of serious adverse event caused by TRP
- If, in light of the circumstances (in particular, non-compliance with TRP) the investigator considers that a continuation of TRP is unfeasible or unacceptable.

The sponsor or investigator decides about withdrawal of patients from further TRP in case of occurrence of criteria mentioned above.

If the patient withdraws from the trial, and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

5.5.2 Handling of Withdrawals

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the patient's medical records. In case of withdrawal of a patient at his/her own request, the reason should be asked for as extensively as possible and documented.

In order to recognize AEs all efforts will be made to follow up the patient and document the AEs.

All ongoing Adverse Events (AEs)/ Serious Adverse Events (SAEs) of withdrawn patients have to be followed up until no more signs and symptoms are verifiable or the patient is in stable condition.

5.5.3 Handling of Pregnancy

In case of incident pregnancy during the course of the study Gardasil® vaccination will be discontinued but patient remains in the study.

Pregnancies should be treated similar to a serious adverse event and notified to the sponsor within the same timelines. The course of the pregnancy should be followed up until delivery or end of any cause and abnormal outcomes should be reported.

5.5.4 Replacement of Patients

Patients will not be replaced.

For details refer to chapter 10 statistical analysis.

5.5.5 Premature Closure of the Clinical Trial or a Single Study Site

The trial can be prematurely closed or suspended by the sponsor in case new findings potentially altering the benefit-risk ratio become known within this trial or other studies. The Ethics Committees (EC) and the competent regulatory authorities must then be informed. Furthermore, the Ethics Committees and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (completed, partially completed, and blank CRFs, randomization envelopes, investigational medicinal products, etc.) must be returned to the sponsor

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all study sites and investigators.

The sponsor has the right to close a study site, at any time, in case of:

- non-compliance with the protocol
- slow recruitment
- poor quality data
- excessive toxicity

5.6 Prior and Concomitant Illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and will be documented on the appropriate pages of the CRF. Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

5.7 Prior and Concomitant Medication

Relevant additional medication administered to the patients up to 90 days prior to visit 1 are regarded as pre-medication and any additional medication administered at any time during the trial are regarded as concomitant medication and must be documented on the appropriate pages of the CRF.

6 Investigational Medicinal Product/-s

6.1 General Information about Investigational Medicinal Product/-s

Investigational medicinal product:

Drug Code:	Gardasil®
International Nonproprietary Name (INN):	Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant
ATC code, if officially registered:	J07BM01
Pharmaceutical formulation:	Injection/Shot
Route of administration:	i.m.
Storage conditions:	2-8°C
Manufacturer / Importer:	Sanofi Pasteur MSD
Licence Number	EU/1/06/357/003

Placebo

Drug Code:	Isotonic saline 0,9 %
International Nonproprietary Name (INN):	NaCl
ATC code, if officially registered:	none
Pharmaceutical formulation:	Injection
Route of administration:	i.m.
Storage conditions:	None
Manufacturer / Importer:	Eifelfango® Chemisch Pharmazeutische Werke

6.2 Therapeutic Effects

Gardasil® is a vaccine indicated in girls/women and boys/men as of age 9 years and older for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- precursors of malignant genital lesions (cervix, vulva and vagina) and cervical cancer
- genital warts (condylomata acuminata)

6.3 Known Side Effects

The most common known side effects are described in the current SPC version (April 2012) of Gardasil®. The effective SPC version will be provided to the investigators with the documents in the ISF.

6.4 Dosage Schedule

6.4.1 Dosage

0.5 ml suspension for intramuscular injection according to manufacturer's schedule: 0, 2, 6 months.

6.5 Treatment Assignment

The study medication will be administered only to patients included in this study. It will be administered according to SPC. Placebo (NaCl) will also be administered according to the SPC of Gardasil® (month 0, 2, 6).

Patients withdrawn from the study retain their identification codes (e.g. randomization number, if already given). New patients must always be allotted a new identification code.

6.6 Randomization and Blinding

All patients who enter into the screening period of the study (defined as the point at which the patient signs the informed consent) will receive a unique patient identification number before any study procedures are performed. This number will be used to identify the patient throughout the clinical study and must be used on all study documentation related to the patient. Clinical sites must complete the screening case report forms for all registered patients, even if the patient is not treated in this study.

Investigators participating in assessment and clinical care of study patients remain blinded with respect to the study medication (Gardasil® or placebo). Therefore, an unblinded person (either a medical doctor or a qualified study nurse), not involved in assessment and clinical care of study patients, has to apply the study medication. The unblinded person is obliged to keep secrecy about the supplied study medication and related documentation (see also section 6.8.).

Upon confirmation of eligibility (patients must meet all inclusion criteria and must not have any exclusion criteria), the unblinded person must contact a centralized internet randomization system (www.randomizer.at). A patient is considered enrolled when he or she has been randomized to receive either Gardasil® or placebo.

Patients will be randomized to one of two arms in a 1:1 ratio and stratified by site. The syringes for study medication injections have to be blinded to the patient with an opaque label by the unblinded person. At the end of visit 4 (month 12) the unblinded person will inform the patient whether he or she has received Gardasil® or placebo. For patients of the Gardasil® arm vaccination information will be transferred to their personal immunization card. Patients of the placebo arm will be offered to receive Gardasil® by the unblinded person and outside the study protocol. The other clinical personnel shall remain blinded to the identity of the treatment from the time of randomization until final database lock.

The randomization scheme will be generated by an online randomization provider (randomizer.at) using a validated system and will be reviewed and approved by a member of the biostatistics group of the NCT study center. At the end of the study and after data verification and database lock, the assigned blinded codes can be broken for the final analysis of study data.

6.7 Packaging and Labelling

The study medication will be labelled according to § 5 (8) of GCP-V, i.e. there is no need for a specific label as the study medication is market approved. The study medication will be administered directly to the patient and will not be dispensed to the patient.

6.8 Supplies and Accountability

Gardasil® will be purchased from the local pharmacy of the study sites as commercial product and will be reimbursed by the sponsor. Gardasil® must be stored in accordance with manufacturer's instructions at 2-8°C and dry. Placebo (isotonic NaCl solution 0,9%) will be ordered by the sponsor and sent to the study sites, and the injection will be prepared individually for this study by the unblinded person. 0.5 ml of NaCl will be applied by single use syringe and applied to the patient who will receive placebo. The unblinded person will stick an opaque label to the syringe prior to injection. Gardasil® or placebo will only be administered by the unblinded person. It is not at all allowed that the injection will be administered by the investigator who is treating the patient. The unblinded person will keep account of Gardasil® and placebo administered to the patient. This documentation will be filed in a separate folder not accessible to the blinded personnel.

There will be a separate part of the CRF where the unblinded person will document for each randomized patient the random number, the date of injection, injection site and Adverse Events which occurred during vaccination. The blinded personnel at the study site will have no access to this part of the CRF.

Drug accountability has to include date of dispensary, patient identification, lot number/ Gardasil® label or other identification of study medication. The site monitor will check the documentation to ensure the correct accountability of all study medication used.

6.9 Compliance

Gardasil® or placebo will be directly administered i.m.

7 Study Methods

The investigative team at each study site will be responsible for performing all evaluations and recording information in the medical record as well as completing the CRF.

7.1 Description of Study Visits

Treatment as well as routine and study specific examinations will be conducted according to the study schedule (p. 11). Study visits are scheduled as in-person visits at the study site. After the screening visit, a visit window +/- 4 weeks is allowed for visit 2 and 4, and 8 weeks for visit 3.

Importantly, the patients have to be observed closely for 30 minutes after each administration of vaccine and appropriate medical treatment should be available in case of an anaphylactic reaction.

The maximum duration of the entire study for a patient will be approximately 12 months consisting of 4 visits. The patients of the placebo group will be offered to receive Gardasil® at their last visit (month 12) outside the trial protocol. Assessments and procedures by visit are provided in the following sections.

7.1.1 Screening evaluation

Patients will be screened for eligibility. Screening evaluations and procedures could be performed at the same day as visit 1 or up to 7 days prior to visit 1. At the screening visit the following procedures will be performed:

- Written informed consent
- Check inclusion / exclusion criteria
- Demographics (gender/year of birth/country of birth)
- Negative pregnancy status for WOCBP (ask for information)
- Medical history (including allergies)
- Diagnosis of recurrent external condylomata acuminata
- Physical examination (detailed description see 7.2)

If all inclusion and exclusion criteria are met the patient will be randomized at visit 1.

7.1.2 Visit 1 (Month 0)

Visit 1 includes the following procedures:

- Final assessment of eligibility criteria
- Patients Characteristics (Smoking status / number of sexual partners within the last 12 months)
- Prior medication (up to 90 days prior to visit 1) to identify patients who have received immunomodulators
- negative pregnancy urine test for WOCBP prior to the vaccination
- Swabs (detailed description see 7.2)
- Biopsy prior to ablation
- Blood sample (2 ml) before the vaccination given to determine HPV serology
- If the patient has signed the informed consent form for the HPV T cell analysis an extra blood sample (2x10 ml; total 20 ml) will be taken
- Randomization (performed by unblinded personal)
- Vaccination with Gardasil® or placebo
- Assessment of Adverse Events (during vaccination and 30 min observation period by unblinded personal)
- Assessment of concomitant medication

7.1.3 Visit 2 (Month 2) and Visit 3 (Month 6)

Visit 2 and 3 include the following procedures:

- Physical examination
- negative pregnancy urine test for WOCBP prior to the vaccination
- Swabs
- In case of recurrence of condylomata acuminata, biopsy will be repeated before ablation of recurrent condylomata acuminata
- Blood sample (2 ml) to determine HPV serology
- Vaccination with Gardasil® or placebo
- Assessment of Adverse Events (during vaccination and 30 min observation period by unblinded personal)
- Assessment of concomitant medication

7.1.4 Visit 4 (Month 12) / End of study or early discontinuation visit

6 months after the last vaccination visit 4 will take place. This will be the end of study visits.

If a patient did not show up for all 3 vaccination visits every attempt should be made to perform the procedures of visit 4, 6 months after the last vaccination. The reason for early discontinuation shall be documented.

The following procedures will be performed at visit 4:

- Physical examination
- Pregnancy status (ask for information)
- Swabs

- In case of recurrence of condylomata acuminata, biopsy will be repeated before ablation of recurrent condylomata acuminata
- Blood sample (2ml) to determine HPV serology
- If the patient has signed the informed consent form for the HPV T cell analysis an extra blood sample (2x10 ml; total 20 ml) will be taken.
- Assessment of all adverse events which occurred until this visit
- Assessment of concomitant medication since the last vaccination
- Patients who were randomized to placebo group will be offered to receive Gardasil® and if consenting they will receive the first vaccination at the end of this visit. This vaccination will be performed outside the trial protocol in compliance with the SPC and according to the discretion of the treating physician.

7.2 Methods of Sample Collection and Examination

Diagnosis of condylomata acuminata will be based on clinical criteria and will be performed by the investigator at each study site. Clinical diagnosis of condylomata acuminata will be verified by biopsy and histology as described below.

7.2.1 Physical examination

The physical examination consists of inspection of external genital regions including labia minora and majora, introitus vaginae, clitoris, prepuce, glans penis, coronal sulcus and frenulum, perianal skin, perineal region, inguinal and pubes region. Palpation of inguinal lymph nodes will also be done.

7.2.2 Swab

A swab will be taken of the lesion and an additional swab of a non-lesion surface preferentially contralateral to the lesion and at least 5 cm outside of the lesion area.

If skin contact examination devices (dermatoscope) are used, swabs have to be taken first and appropriate cleaning protocols in between patients have to be applied to the device.

Swab samples will be stored at 4° C and shipped once a month to DKFZ. DKFZ will extract DNA from swab samples and analyze for presence of 51 mucosal HPV, including HPV 6 and 11, and for cutaneous HPV as described in Schmitt et al., 2008, Schmitt et al., 2011; Michael et al., 2011.

7.2.3 Biopsy

5mm punch or scissors excision will be taken from the lesion prior to ablation to investigate histology and molecular marker.

Biopsy tissue will be formalin-fixed and paraffin-embedded (FFPE) and processed for routine histology by the local pathology departments. After local histological diagnoses slides will be sent to the Department of Dermatology und Venerology, University of Rostock for rereading to ensure homogenous histology diagnosis within the study. After rereading took place the slides will be sent back to the study site of origin.

Remaining FFPE blocks will be sent from the study sites to DKFZ every 3 months. DKFZ will extract DNA from additional sections and analyze for presence and type of 51 mucosal HPV, including HPV 6 and 11, and for cutaneous HPV as described in Schmitt et al. 2008; Schmitt et al., 2011; Michael et al., 2011. Remaining FFPE blocks will be sent back to the study site of origin.

7.2.4 HPV Serology

Blood samples for serology will be sent within 24h only Monday to Thursday by ordinary mail in a pre-addressed envelope to DKFZ. Detailed shipping information will be provided in the ISF.

HPV-specific antibodies for a variety of HPV types, including all vaccine types and for specificity controls, also antibodies to other infectious agents will be determined by multiplex serology as described in Waterboer et al., 2005; Michael et al., 2008.

7.2.5 T-cell analysis

For HPV-specific T-cell analyses full blood samples (2x10 ml, Li-Heparin) will be collected at visits 1 and 4 and shipped at ambient temperature the same day with overnight express courier to the laboratory at Charité Berlin. In exceptional cases (blood sampling was performed after closure of post offices) blood samples can be stored at room temperature at the study site for a maximum of 15 hours before shipment. Blood samples shall never be cooled.

The laboratory at Charité will perform direct ex-vivo stimulation assays and flow cytometric (FACS) analyses as described in Frentsch et al., 2005.

8 Plan for Treatment or Care after the Study

After the study ends patients of the Gardasil® arm will be treated according to conventional treatment guidelines for condylomata acuminata (Gross G et al. www.awmf.org, 2008). At visit 4 (month 12) patients of the placebo arm will be additionally offered Gardasil® vaccination outside the trial protocol.

9 Assessment of Safety

9.1 Definitions

9.1.1 Adverse Events

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a patient administered a pharmaceutical product even if it does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Intercurrent diseases and accidents
- Worsening of medical conditions/ diseases existing before clinical study start
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the study.

AEs are classified as "non-serious" or "serious".

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the patient was at risk of death at the time of event and not to an event which hypothetically might have cause death if it was more severe)
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity or
- Is a congenital anomaly/ birth defect.
- Is otherwise medically relevant

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations - such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

All surgical interventions/hospitalizations that had been scheduled prior to enrolment and which are carried out during the course of the study are not considered as SAE.
The ablation of the genital warts is also not considered as SAE and does not need to be reported.

9.1.3 Expectedness

An ‘unexpected’ adverse event is one the nature or severity of which is not consistent with the applicable product information: Summary of Product Characteristics (SPC). Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute ‘unexpected’ events.

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to IMP and ‘unexpected’, i.e. the nature and/ or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case, either the investigator who primary reported the SAE or the second assessor classify the SAE as ‘suspected’ i.e. either as related or probable or possible related to IMP and the SAE is unexpected it will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent higher federal authority (PEI) and to all participating investigators.

9.2 Period of Observation and Documentation

All AEs reported by the patient or detected by the investigator, will be collected during the study and must be documented on the appropriate pages of the CRF. AEs must also be documented in the patient’s medical records.

In this study, all AEs that occur during or after the first vaccination will be documented on the pages provided in the CRF. All patients who have AEs, whether considered associated with the use of the study medication or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition.

9.2.1 Intensity of AEs

The intensity of an AE should be assessed by the investigator as follows:

mild: temporary event which is tolerated well by the patient.

moderate: event which results in discomfort for the patient and impairs his/ her normal activity.

severe: event which results in substantial impairment of normal activities of patient.

9.2.2 Coherency between AEs and the IMP

The investigator will evaluate each AE that occurred after administration of investigational medicinal product regarding the coherency with the administration of the investigational medicinal product possibly:

related: There is a reasonable possibility that the event may have been caused by IMP. A certain event has a strong temporal relationship and an alternative cause is unlikely.

probable: An AE that has a reasonable possibility that the event is likely to have been caused by IMP. The AE has a timely relationship and follows a known pattern of response, but a potential alternative cause may be present.

possible: An AE that has a reasonable possibility that the event may have been caused by IMP. The AE has a timely relationship to the IMP; however, the pattern of response is untypical, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.

unlikely: Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.

not related: An AE that does not follow a reasonable temporal sequence related to IMP and is likely to have been produced by the patient's clinical state, other modes of therapy or other known aetiology.

9.2.3 Outcome of AEs

The outcome of an AE at the time of the last observation will be classified as:

Recovered/ resolved all signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation.

Recovering/ resolving the intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution.

Not recovered/ not resolved signs and symptoms of an AE are mostly unchanged at the time of the last interrogation.

Recovered/ resolved with sequel actual signs and symptoms of an AE disappeared but there are sequels related to the AE.

Fatal resulting in death. If there are more than one adverse event only the adverse event leading to death (possibly related) will be characterized as 'fatal'.

Unknown the outcome is unknown or implausible and the information cannot be supplemented or verified.

9.2.4 Action taken with the IMP

The action taken with IMP will be assigned to one of the following categories:

Dose not changed no change in the dose of IMP

Drug withdrawn discontinuation of IMP

9.2.5 Countermeasures

The term 'Countermeasures' refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. Following categories will be used to categorize the countermeasures to adverse events:

None no action taken

Drug treatment newly-prescribed medication or change in dose of a medication

Others other countermeasures, e.g. an operative procedure

9.3 Reporting of Serious Adverse Events by Investigator

All SAEs must be reported by the investigator to the responsible Safety Officer at the KKS Heidelberg as soon as possible but no later than 24 hours after the SAE becomes known using the "Serious Adverse Event" form. The reporting will be performed by faxing of a completed SAE form to the following fax number:

06221- 56-33725

The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the study medication. SAEs will be reported from the timepoint of the first administration of study medication (vaccination) until visit 4 (month 12). For patients who were randomized in the placebo group, and receive Gardasil® after placebo, all SAEs will be ascertained in an extended observation period until their last visit (visit 6; month 18).

All SAEs will be subject to a second assessment by a designated person. The designated person for the present study, referred to as the second assessor is:

PD Dr. Carsten Kempkensteffen; Phone: +49 (0)30/8445-2577 , Fax: +49 (0)30/8445-4620

The second assessor will fill out a 'Second Assessment Form' for each SAE and send it back per fax to the responsible person at the KKS Heidelberg within 48 hours, fax-number:

06221- 56-33725

The 'Second Assessment Form' will contain the following information:

I) assessment of relationship between SAE and IMP

II) assessment of expectedness of SAE (derived from IB or SPC)

III) statement if the benefit/ risk assessment for the study did change as a result of SAE.

In case of a pregnancy occurring during the study, or up to 6 month after the end of the study in case of Gardasil® administration to the placebo group, the pregnancy should be treated similar to a SAE and notified to the sponsor within the same timelines.

The investigator has to fill out the provided pregnancy reporting sheet as complete as possible and send it to the above mentioned number.

The course of the pregnancy should be followed up until delivery or end of any cause. Any abnormal outcome should be reported and include an assessment of the relationship to the IMP.

SAEs occurring during pregnancy must be reported on the SAE Report Form according to the requirements given above.

The investigator has to fill out the provided pregnancy reporting sheet as complete as possible and send it to the above mentioned number.

The course of the pregnancy should be followed up until delivery or end of any cause. Any abnormal outcome should be reported and include an assessment of the relationship to the IMP.

SAEs occurring during pregnancy must be reported on the SAE Report Form according to the requirements given above.

9.4 Expedited Reporting

SUSARs are to be reported to the ethics committee(s), regulatory authorities (PEI) and to all participating investigators within regulative defined timelines, i.e. they are subject to an expedited reporting. All principal investigators of each reporting site are obliged to inform their study team about all SUSARs.

The expedited reporting will be carried out by a responsible Safety Officer at the KKS Heidelberg. If applicable, the Safety Officer will break the blind. Only SUSARs occurring after administration of IMP will undergo expedited reporting.

In case of a SUSAR after administration of placebo a decision regarding the need of expedited reporting will be taken by the medical expert (second assessor).

In the case of SUSARs that resulted in death or were life-threatening the competent authority, the Ethics Committee, and all principal investigators must be notified as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the competent authority and the ethics committees within an additional eight calendar days. All other SUSARs and safety issues must be reported to the competent authority and the ethics committees as soon as possible but no later than 15 calendar days after safety officer has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible. Person-related data have to be pseudonymized by using a participant code number.

Each SUSAR has to be reported as a single case to the competent authority and the ethics committee. Expedited reporting is not usually required for reactions which are serious but expected.

9.5 Emergency Unblinding

If it is medically imperative to know what study medication the patient is receiving, the principal investigator or authorized person of each site should break the blind. The principal investigator or the person who breaks the blind must record the date and the reasons for doing so in the CRF, in the patient's medical record. Whenever possible, the Coordinating Investigator should be contacted before the blind is broken.

9.6 Emergency Treatment

During and following a patient's participation in the study, the investigator should ensure that adequate medical care is provided to a patient for any AE including clinically significant

laboratory values. The investigator should inform a patient when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

10 Statistical Considerations

10.1 Study Hypothesis

The hypotheses of interest are:

H_0: $RR_{Gardasil®}$ - $RR_{Placebo}$ eq 0 versus H_1: $RR_{Gardasil®}$ - $RR_{Placebo}$ ne 0,

where $RR_{Gardasil®}$ is the probability of recurrence on Gardasil® and $RR_{Placebo}$ the probability of recurrence on placebo.

10.2 Sample Size Calculation

The primary analysis will be a comparison of the recurrence rates in the two arms. Based on previously published experience (Zhang et al., 2000) we expect at least a 25% difference in the recurrence rates between Gardasil® and placebo. The sample size is calculated using nQuery advisor® and with the following assumptions:

- α, the probability of type I error: 5%, two sided
- β, the probability of type II error: 10%; Power: 90%
- Proportion of recurrence in Gardasil® arm: 25%
- Proportion of recurrence in Placebo arm: 50%
- Equal group allocation (1:1)
- Two group continuity corrected Chi ^{2}-test of equal proportions (odds ratio = 1) (equal n's)

Under the above assumptions a sample size of 85 in each group will provide 90% power to detect a treatment difference from 25% on placebo to 50% on Gardasil®. Assuming, that about 15% of the patients randomized to the study will drop-out, a total of 100 patients per treatment arm is needed.

10.3 Analysis Variables

10.3.1 Primary Efficacy Endpoint

The primary endpoint of this study is the recurrence rate, defined as the proportion of patients with recurrence, where recurrence is defined in Section 2.1.

10.3.2 Secondary Efficacy Endpoints

- 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 and visit 4)
- Associations between immunological and clinical outcomes

10.3.3 Safety Endpoints

The primary safety endpoint will be assessed by reporting of all Treatment Emergent Adverse Events (TEAE) defined as AEs occurring or worsening after the start of the first study treatment. For definitions of the safety endpoints ref. Section 9.

10.3.4 Covariate and subgroup definitions

The following covariates will be used in the statistical analysis and may also be used to produce subgroup summaries:

- Age
- Gender
- Smoker (yes/no)
- Country of birth
- HPV 6/11- Status (presence of HPV 6/11 DNA)
- Number of sexual partners in the last 12 months

10.4 Analysis Populations

The Full Analysis Set (FAS) includes all randomized patients. Following the intention-to-treat principle, patients are analyzed according the treatment that they were assigned to at randomization. The FAS will be used for the primary analysis of efficacy.

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.

Safety Population: The safety population includes all patients who have received at least one dose of study treatment. Patients who received study treatment different from their initial randomized treatment will be included in the safety population under the treatment that they received.

10.5 Statistical Methods

10.5.1 General Considerations

The statistical analysis will be carried out by the responsible biostatistician at Clinical Trial Center of the National Center for Tumor Diseases (NCT) Heidelberg using the SAS statistical software [SAS Institute Inc., Cary, NC, USA] or comparable software. The analysis will be done as soon as the database has been declared to be complete and accurate, and has been locked. The details of the analysis will be laid out in the statistical analysis plan, which will be finalized and approved prior to the database lock. It has to be authorized before by the biometrician and the Coordinating Investigator.

10.5.2 Demographic and other Baseline Characteristics

Descriptive statistics will be provided to summarize demographics and baseline characteristics using the FAS. Categorical variables will be summarized for each treatment group by frequency and its corresponding percentage. Quantitative variables will be summarized for each treatment group using appropriate descriptive statistics i.e. mean, median, standard deviation, minimum, maximum.

10.5.3 Study Treatment and Concomitant Therapies

Summary statistics will be presented by treatment group for the cumulative doses of study treatments received. The number of patients with dose modifications/ interruptions and drop-out from the study treatment will be presented by treatment group. Reasons for the deviations from the planned administration will be tabulated.

Concomitant medications taken concurrently with the study medication will be tabulated. These tables will include medications starting on or after the start of study treatment or medications

starting prior to the start of study treatment and continuing after the start of study treatment. Concomitant medications or non-drug therapies starting and ending prior to the study treatment will be listed. The safety population will be used for all above-mentioned tables and listings.

10.5.4 Efficacy Evaluation

Analysis of the Primary Endpoint

The primary analysis will be a comparison of the recurrence rates in the two arms using a two-sided Cochran-Mantel-Haenszel (CMH) test (Agresti, 2002). The analysis will be adjusted for study site effects. Summary tables will present the number of patients observed with recurrence, the corresponding percentages and exact 95% confidence interval (Clopper and Pearson, 1934).

The analysis of the primary endpoint will be performed using the FAS. Inferences regarding superiority will be based on the p-value and the confidence interval**.**

Analysis of the Secondary Endpoints

- 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 further explored using a logistic regression model to investigate the effect of the covariates of interest on the recurrence rate and the homogeneity of the treatment effect. The model will include terms for treatment, center and relevant covariates (i.e. age, gender, age, smoker, country of birth, HPV6/11-Status, number of sexual partners in the last 12 months). Odds ratios with exact 95% CI will be used as a measure of association between treatment and recurrence.
- For the time-to-event type efficacy measure (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. The above method relies on the assumption that events are recorded at the time they occur and there is no lag in the time at which they are reported. If this assumption is not satisfied, an alternative, interval censored analysis will be used.
- All other secondary variables will be analyzed using descriptive and explorative methods. Continuous variables will be summarized using standard summary statistics as appropriate. Summary statistics for categorical variables will include frequency counts and percentages. If appropriate, graphical presentations of data will be created. Appropriate confidence intervals of estimates of effect will be given to quantify the degree of uncertainty of these estimates.

10.5.5 Safety Evaluation

All safety analyses will be performed for the safety population.

Analysis of Adverse Events

Adverse Events will be coded with the MedDRA dictionary. Frequencies of patients experiencing at least one TEAE will be displayed. Detailed information collected for each TEAE will include: A description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Summaries of incidence rates (frequencies and percentages) of TEAEs by MedDRA System Organ Class (SOC) and Preferred Term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by intensity and TEAEs by relationship to study drug. Summary tables will present the number of patients observed with TEAEs, the corresponding percentages, and exact 95% CI.

Other Analyses

Patient Disposition (the number of patients enrolled, treated, and in the analysis populations) will be tabulated. In addition, the number of patients who withdrew from the study and reasons for discontinuation will be summarized.

10.5.6 Handling of Missing Values

Patients with unknown recurrence status at the end of blinded period (visit 4), the last known status will be taken from laboratory assessment /serological response or any other relevant information (may send out special queries to obtain more up to date status information). In order to investigate the robustness of the results, supportive analyses will be performed to investigate the sensitivity of the results in the primary analysis to the handling of missing values. A full description of the sensitivity analyses will be given in the statistical analysis plan and will be documented in the statistical report and included in the final study report.
For patients with incomplete follow-up, time to last follow-up date will be used as the censoring time in the analysis of time-to-event data.

Other missing data will be shown as missing on appropriate tables and listings.

10.6 Interim Analyses

No interim analyses are planned for the present study.

11 Data Management

11.1 Data Collection

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to a paper form.

All findings including clinical and laboratory data will be documented by the investigator or an authorized member of the study team in the patient's medical record and in the CRF. The investigator and the unblinded person are responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data. The CRF has to be filled out according to the specified CRF Completion Guidelines.

The correctness of entries in CRF will be confirmed by dated signature of the responsible investigator or respectively the unblinded person. The original CRF will be timely transferred to the data management of NCT Clinical Trial Center, one copy will remain at the study site.

11.2 Data Handling

After receipt of the CRF-pages and the laboratory data at the data management of NCT Clinical Trial Center, all data as recorded in the CRF will be entered in a database. In order to ensure that the database reproduces the CRFs correctly, the NCT accomplishes a double entry of data. The completeness, validity and plausibility of data are examined by validating programs, which thereby generate queries.

All missing data or inconsistencies will be reported back to the site(s) and clarified by the responsible investigator. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

All data management activities will be done according to the current Standard Operating Procedures (SOPs) of the NCT Clinical Trial Center.

11.3 Storage and Archiving of Data

According to §13 of the German GCP-Regulation all important study documents (e.g. CRF) will be archived for at least 10 years after the study termination.

The investigator(s) will archive all study data (source data and Investigator Site File (ISF) including patient identification list and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations. The Patient Identification List will be archived for at least 15 years after the study termination.

If the investigator relocates, retires, or for any reason withdraws from the study, the NCT Clinical Trial Center should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the NCT Clinical Trial Center. The investigator must obtain NCT's written permission before disposing of any records, even if archiving requirements have been met.

12 Ethical and Legal Aspects

12.1 Good Clinical Practice

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that all persons involved in the study abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The study will be carried out in keeping with local legal and regulatory requirements.

12.2 Patient Information and Informed Consent

Before being admitted to the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. The patient must give consent in writing. The personally signed and dated Informed Consent Form must be kept on file by the investigator(s), and documented in the case report form.

A copy of the signed informed consent document must be given to the patient. The documents must be in a language understandable to the patient and must specify who informed the patient.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue the study.

12.3 Confidentiality

The data obtained in the course of the study will be treated pursuant to the Federal Data Protection Law (Bundesdatenschutz- bzw. Landesdatenschutzgesetz, BDSG, LDSG) as well as to §40 (2a) AMG.

During the clinical study, patients will be identified solely by means of their year of birth, and an individual identification code (Patient ID). Study findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The patient consents in writing to relieve the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, inspectors) may inspect the patient-related data collected during the study ensuring the data protection law.

The investigator will maintain a patient identification list (patient IDs with the corresponding patient names) to enable records to be identified.

Patients who did not consent to circulate their pseudonymized data will not be included into the study.

12.4 Responsibilities of Investigator

The principal investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions, as outlined in this protocol and in the GCP-Regulations.

The principal investigator should maintain a list of investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

12.5 Approval of Study Protocol and Amendments

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) as well as to the competent federal authority (PEI). A written favourable vote of the EC and an (implicit) approval by the competent higher federal authority are a prerequisite for initiation of this clinical study. The statement of EC should contain the title of the study, the study code, the study site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first patient is enrolled in the study, all ethical and legal requirements must be met. All planned substantial changes (see §10, (1) of German GCP-Regulation) will be submitted to EC and the competent higher federal authority in writing as protocol amendments. They have to be approved by the EC and the competent higher federal authority.

The investigator and the sponsor will keep a record of all communication with the EC and the regulatory authorities.

12.6 Continuous Information to Independent Ethics Committee

Pursuant to the German Drug Law (AMG) and the GCP Regulation, the EC and the competent higher federal authority will be informed of all suspected serious unexpected adverse reactions (SUSARs) and all AEs resulting in death or being live-threatening occurring during the study. Both institutions will be informed in case the risk / benefit assessment did change or any others new and significant hazards for patients' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year – Development Safety Update Report (DSUR).

The EC and the regulatory authorities must be informed of the end of the study. They will be provided with a summary of study results within one year after the end of the blinded clinical period (LPO).

12.7 Notification of Regulatory Authorities

The local regulatory authorities as responsible for each particular investigator and the competent higher federal authority will be informed before the beginning, during and at the end of the study according to §67 AMG and §13 GCP-V. Each investigator is obliged to notify his/ her local regulatory authority and the competent higher federal authority according to §67 AMG and §12 (1, 2, 6). This responsibility could be delegated to the sponsor by signing an authorization sheet and providing all relevant documentation.

12.8 Registration of the Trial

Prior to the beginning of the clinical period (FPI) of the study the authorized representative of the sponsor will register the study at a public accessible clinical trial register having the status of a primary register according to the International Clinical Trials Registry Platform (ICTRP) and correspondingly is listed at the International Clinical Trials Registry Platform of the World Health Organisation (WHO, www.who.int/ictrp/en/).

The registration is a prerequisite for a publication in many peer-reviewed journals (see Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (http://www.icmje.org/ publishing_10register.html)). The requirements are fulfilled by the European Clinical Trials Register and submission of EMA Modul 1 (Clinical Trial Application Form). Other appropriate registers are e.g.: www.ClinicalTrials.gov, Current Controlled Trials (www.controlled-trials.com/), German Clinical Trials Register (DRKS, https://drks-neu.uniklinik-freiburg.de/drks_web/).

12.9 Insurance

According to § 40 AMG, the sponsor has to subscribe to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards. The insurance was taken out at HDI-Gerling Versicherung AG (insurance number: 5701032703012, registration number: 1404 2012 102, maximum limit: € 500.000 per participating person).

Any impairment of health which might occur in consequence of study participation must be notified to the insurance company. The patient is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the study, the patient must not undergo other clinical treatment except for cases of emergency. The patient is bound to inform the investigator immediately about any adverse events and additionally drugs taken.

The insurance company has to be informed about all amendments that could affect patients' safety.

13 Quality Assurance

13.1 Monitoring

Monitoring will be done by personal visits from a clinical monitor according to SOPs of the KKS Charité Berlin. The monitor will review the entries into the CRFs on the basis of source documents. This will require direct access to all original records for each patient (patient charts, laboratory reports, etc.). The investigator must allow the monitor to verify all essential documents and must provide support at all times to the monitor.

It is the monitor's responsibility to inspect the case report forms at regular intervals throughout the duration of the study to verify adherence to the protocol; completeness, accuracy and consistency of the data.

By frequent communications (letters, telephone, fax), the site monitor will ensure that the study is conducted according to the protocol and regulatory requirements.

13.2 Inspections / Audits

Regulatory authorities and an auditor authorized by the sponsor may request access to all source documents, CRF, and other study documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities.

14 Agreements

14.1 Financing of the Study

The study will be financed using funds of DKFZ.

A clinical study agreement with the sponsor will be signed by the investigator and legal representative of each site and the administrative representative of the sponsor, prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will be fixed in the clinical study agreement.

14.2 Financial Disclosure

Before the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsors/ a funding company, in the investigational product(s) or any commercial organisation being involved in the clinical study. The investigator has also to confirm that he/she has not entered into any financial arrangement whereby the value of compensation paid could affect the outcome of the clinical study.

The investigator agrees to update this information in case of significant changes.

14.3 Reports

A final clinical study report will be prepared according to the ICH GCP guideline on Structure and Contents of Clinical Study Reports (E3) after the last patient has completed the last visit (visit 4). A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated.

14.4 Publication

All data collected in the course of the study are property of the sponsor (DKFZ) of the study.

Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by involved investigators or their representatives will require review and approval by the authorized representative of the sponsor.

All information concerning the study is confidential before publication.

15 Signatures

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal product
- the moral, ethical, and scientific principles governing clinical research as set out in the guidelines of International Conference on Harmonization (ICH) Good Clinical Practices (GCP).

The investigator will be supplied with details of any significant or new finding including relevant safety information relating to treatment with the investigational medicinal product.

Date: _____ Signature: _____

Name (block letters): Prof. Dr. Lutz Gissmann
Function: Authorized representative of the sponsor

Date: _____ Signature: _____

Name (block letters): PD Dr. Carsten Kempkensteffen
Function: Coordinating Investigator

Date: _____ Signature: _____

Name (block letters): Irini Karapanagiotou-Schenkel
Function: Biostatistician

16 Declaration of Investigator

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I pledge that all persons assisting with the study are qualified and adequately informed about the protocol and study related procedures.

I will enrol the first patient only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for study participation from all patients.

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I pledge to retain all study-related documents and source data as described.

Date: _____ Signature: _____

Name (block letters): _____

Study Site (address): _____

_____

_____

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