# Tolerance and immunogenicity of ProCervix, a therapeutic vaccine composed of 2 Human Papillomavirus (HPV) antigens vectored in recombinant adenylate cyclases, in HPV 16 and/or HPV 18 infected women with normal cytology

Published: 26-09-2011
Last updated: 28-04-2024

Primary objective: * Examine the safety and tolerability, both local and general, of ProCervix Solution (escalating doses) and ProCervix Powder in women infected by HPV 16 and/or 18 with normal cytology from Week 0 to Week 10. Secondary objectives...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Viral infectious disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON35990

**Source**
ToetsingOnline

**Brief title**
Tolerance and immunogenicity of ProCervix, a HPV-16 /18 therapeutic vaccine

### Condition

- Viral infectious disorders
- Female reproductive tract infections and inflammations

**Synonym**
HPV16 and/or HPV18 infection

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Genticel, Pasteur-BioTop
**Source(s) of monetary or material Support:** Genticel SA

## Intervention

**Keyword:** HPV16 / HPV18, normal cytology, ProCervix, therapeutic vaccin

## Outcome measures

**Primary outcome**

Safety:

- treatment-emergent adverse events (AEs) including serious adverse events

(SAEs)

- treatment-emergent changes in clinical laboratory tests,

- vital signs

- physical examinations

- exams directed at the vaccination site

- observations on the status of HPV 16 and HPV 18 infection

- cytology in cervical scrapings from before and after exposure to ProCervix

Immunogenicity:

- tests of humoral immunity to HPV

- test of cellular immunity to HPV

- assessment of cellular immune response (changes in peripheral blood [PB]

T-cell responses to the E7 antigen of HPV 16 and HPV 18)

- evaluation of serologic response (changes in anti-HPV 16 E7 and anti-HPV 18

E7 antibody titres)

**Secondary outcome**

Immunological assessments other than the antigen specific measures listed above

will be evaluated in subjects using available material from preserved

peripheral blood mononuclear cells, plasma and cervical samples, to

characterize immunological responses to ProCervix.

# Study description

**Background summary**

Cervical cancer is the second most common malignancy among women worldwide, with approximately 500,000 new cases diagnosed each year, and about 275,000 deaths per year.

Human Papillomavirus (HPV) infection with certain high risk subtypes is a prerequisite for the development of cervical cancer and HPV is detected in 99.7% of cervical carcinomas. Human Papillomavirus 16 and HPV 18 (the two genotypes targeted by the ProCervix vaccine) are the most common genotypes associated with cervical cancer. They are present as either single or multiple infections in at least 70% of squamous cell carcinoma and 84% of adenocarcinomas of the cervix.

It is thought that the integration of HPV DNA into the human genome is an important (but not essential) step for persistent transcription of E6 and E7 genes. These oncogenes disrupt normal cell cycle control mechanisms and cause malignant transformation of epithelial cells by inactivation of P53 by E6

protein and/or inactivation of Rb by the E7 protein. Human Papillomavirus 16 and/or HPV 18 infections are more persistent than infections with other genotypes and 50% are still present 12-18 months after detection.

ProCervix is based on a novel potent Ag delivery system: the recombinant adenylate cyclase (CyaA) vector based on the detoxified adenylate cyclase of Bordetella pertussis.

The Investigational Product (IP) consists of two recombinant CyaA proteins, CyaA-HPV16E7 (C16-1) and CyaA-HPV18E7 (C18 1) in a 50/50 ratio (C16C18-1 antigen [Ag] mixture). The HPV E7 protein was chosen as the Ag for these two HPV subtypes because it is a small, well conserved protein with T-helper and cytotoxic T lymphocyte (CTL) epitopes for the most common types of human lymphocyte antigen (HLA). Cellular immunity to HPV-16 E7 has been shown to be associated with clinical and cytological resolution of HPV-induced CIN or vulval intraepithelial neoplasia (VIN), indicating that E7-specific T-cells have a role in the control of HPV disease.

ProCervix is adjuvanted by Aldara*, a cream containing 5% of Imiquimod and approved in the EU and the US for topical treatment of various skin conditions. Functional studies of ProCervix and Aldara* in the TC-1 E7 expressing tumour mouse model support the use of this cream as the ProCervix adjuvant

**Study objective**

Primary objective:
* Examine the safety and tolerability, both local and general, of ProCervix Solution (escalating doses) and ProCervix Powder in women infected by HPV 16 and/or 18 with normal cytology from Week 0 to Week 10.

Secondary objectives:
* Examine the safety and tolerability, both local and general, of ProCervix Solution (escalating doses) and ProCervix Powder in women infected by HPV 16 and/or 18 with normal cytology from Week 10 to Week 26.
* Examine the cellular and humoral immunogenicity of ProCervix in women infected by HPV 16 and/or 18 with normal cytology from Week 0 to Week 26.

**Study design**

This is a phase I, single-centre, open-label (Cohorts 1 and 2), multicentre, randomized, double-blinded, placebo-controlled (Cohort 3), and multicentre, open-label (Cohort 4) study of the safety, tolerability, and immunogenicity of escalating paired doses of ProCervix followed by Imiquimod as a vaccine adjuvant in healthy adult female subjects infected by HPV 16 and/or 18 with normal cervical cytology.

Cohort 1 and 2 interventions have been completed in Belgium and are not applicable to Dutch subjects.
Subjects in Cohorts 3 will be treated with ProCervix in a solution formulation, or placebo;
subjects in Cohort 4 will be treated with ProCervix in a freeze-dried (powder) formulation.

**Intervention**

Cohort 1
* 100 mcg ProCervix (solution) on day 1 and day 42 and Imiquimod on day 1,2, 42 and 43.
Cohort 2
* 600 mcg ProCervix (solution) on day 1 and day 42 and Imiquimod on day 1,2, 42 and 43.
Cohort 3
* 600 mcg ProCervix (solution) on day 1 and day 42 and Imiquimod on day 1,2, 42 and 43 or,
* 600 mcg ProCervix (solution) on day 1 and day 42 and Imiquimod on day 1,2, 42 and 43 or
* Placebo injections on day 1 and 42 and Imiquimod on day 1,2, 42 and 43.

Cohort 4
* 600 mcg ProCervix (powder) on day 1 and day 42 and Imiquimod on dag 1,2, 42 and 43.

Cohort 1 en 2 have been performed in Belgium.
Cohort 3 is being performed in Belgium (recruitment completed).
Cohort 4 will take place in Belgium and the Netherlands (VUmc).

**Study burden and risks**

The intended effect of vaccination with ProCervix is the prevention of progression from cervical infection with papillomavirus (serotype 16 and or 18) to high grade neoplastic lesions and cervical carcinoma. Although the trial population in study PC10VAC01 consists of women at risk because of infection with the relevant strain(s) of Human Papillomavirus, no direct (cancer or cytologically based) or indirect (immunologic) evaluations of the efficacy of human exposure to ProCervix are presently available. The benefits of exposure to ProCervix plus Imiquimod in PC10VAC01 include the altruistic benefit of contributing to research related to the treatment of a life-threatening illness and the unproved possibility of decreasing the chance of development of HPV-related high grade neoplastic lesions and cervical cancer. As noted in the Investigational Medicinal Product Dossier (IMPD) and the DSUR, the observed risks of exposure to ProCervix plus Imiquimod have been limited to effects, primarily local, that were anticipated from prior pre-clinical and clinical

experience. The safety experience of subjects in PC10VAC01 has been reviewed formally on seven occasions by the investigators and other members of the SRC. On each occasion, the reviewers have examined the available safety data with particular attention to the grade 2 and 3 local effects observed after exposure to study vaccine and study cream. On each occasion, the SRC has approved continuation of the trial, indicating support for the potential benefit of ProCervix as an effect that would outweigh the side effects observed in the trial to date.

## Contacts

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**Scientific**
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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

1. Female between the ages of 18 and 45 years (inclusive), in general good health with HPV infection confirmed by 2 genotyping tests showing one or both type 16 and type 18.

2. Subject has two consecutive normal cervical cytological evaluations, separated by 6 weeks to 12 months prior to enrolment.
3. Subject has a normal gynaecologic examination.
4. Subject has employed highly effective contraception for the month prior to the first vaccination and will agree to employ highly effective contraception for at least 4 months after the last vaccination.
5. Subject has a CD4+ total count *500cells/mm3.
6. Subject is in general good health based on medical history and clinically acceptable results, in the judgment of the Investigator, on the following assessments: physical examination, vital signs, clinical chemistry, and haematology.

## Exclusion criteria

1. Subject has a current acute or chronic disease, other than infection with HPV that would increase the expected risk of exposure to ProCervix or Imiquimod or would be expected to interfere with the planned evaluations of response to ProCervix, in the judgment of the Investigator.
2. Subject has prior exposure to HPV prophylactic vaccine.
3. Subject has a history of cancer of the cervix or of untreated high grade abnormal cervical cytological evaluation.
4. Subject has received any prophylactic or therapeutic vaccine within 4 weeks of first vaccination.
5. Subject has current systemic infection or any history of primary or secondary systemic immunosuppression.
6. Subject has a history of severe allergy (requiring hospital care) or history of asthma requiring drug management in the last year.
7. Subject has a history of malignancy.
8. Subject was dosed with another investigational drug within 30 days prior to the Screening Visit.
9. Subject has a known history of hypersensitivity to Imiquimod.
10. Subject has a history of severe reaction to any drug or prior vaccination.
11. Subject has a medical condition with clinical and/or biological consequences judged by the investigator incompatible with vaccination(s).
12. Subject is known to have current infection with any other sexually transmitted infection.
13. Subject has a symptomatic vaginal or genital infection.
14. Subject is pregnant or is nursing.
15. Subject has participated in the past in another clinical trial of vaccination related to infection with HPV.
16. Subject has donated blood or plasma within 60 days prior to the Screening Visit.
17. Subject has a prior exposure to ProCervix.
18. Women negative for one or both HPV genotyping tests.

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 12-01-2012 |
| Enrollment: | 5 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | ALDARA 5% CREAM |
| Generic name: | Imiquimod |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | ProCervix |

# Ethics review

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| Approved WMO Date: | 26-09-2011 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 06-12-2011 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

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| Approved WMO Date: | 02-01-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2010-018629-21-NL |
| CCMO | NL37216.000.11 |