



## Clinical trial results: Quadrivalent HPV vaccination after effective treatment of Anal Intraepithelial Neoplasia in HIV+ men

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2013-002009-70   |
| Trial protocol           | NL               |
| Global end of trial date | 01 November 2019 |

### Results information

|                                   |                                                                     |
|-----------------------------------|---------------------------------------------------------------------|
| Result version number             | v1 (current)                                                        |
| This version publication date     | 07 September 2021                                                   |
| First version publication date    | 07 September 2021                                                   |
| Summary attachment (see zip file) | Paper (AIDS<br>HPV_vaccination_to_prevent_recurrence_of_anal.5.pdf) |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | VACCAIN-P |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02087384 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                 |
|------------------------------|---------------------------------------------------------------------------------|
| Sponsor organisation name    | Academic Medical Center                                                         |
| Sponsor organisation address | Meibergdreef 9, Amsterdam, Netherlands, 1105AZ                                  |
| Public contact               | prof.dr. J.M. Prins, Academic Medical Center, 31 205664380,<br>j.m.prins@amc.nl |
| Scientific contact           | prof.dr. J.M. Prins, Academic Medical Center, 31 205664380,<br>j.m.prins@amc.nl |

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 01 November 2019 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 01 November 2019 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 01 November 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess the efficacy of qHPV vaccination in preventing recurrence of high-grade AIN in HIV+ MSM with CD4 counts >350 x 10E6/l who were successfully treated in the past year for high-grade intra-anal AIN.

Protection of trial subjects:

Regular follow-up at outpatient clinic.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 27 March 2014 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Netherlands: 126 |
| Worldwide total number of subjects   | 126              |
| EEA total number of subjects         | 126              |

Notes:

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**Subjects enrolled per age group**

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|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 120 |
| From 65 to 84 years                       | 6   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Enrolment started on March 27, 2014 and was completed on June 1, 2017

### Pre-assignment

Screening details:

A total of 207 HIV+ MSM were screened for eligibility. One hundred twenty-seven (61.4%) men were enrolled and randomised.

Ineligible (n=80):

- Not meeting inclusion/meeting exclusion criteria (n=77)
- Retracted informed consent (n=1)
- Procedural planning not feasible for patient (n=2)

One patient incorrectly enrolled and excluded

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 126 |
| Number of subjects completed | 126 |

### Period 1

|                              |                                                 |
|------------------------------|-------------------------------------------------|
| Period 1 title               | overall trial (overall period)                  |
| Is this the baseline period? | Yes                                             |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

Vaccine or placebo prepared by pharmacy.

### Arms

|                              |      |
|------------------------------|------|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | qHPV |

Arm description:

qHPV L1 virus-like particle (VLP) vaccine (Gardasil-4®, Merck Sharp & Dohme (MSD), Kenilworth, NJ, USA) or a placebo (0.9% saline). The first qHPV or placebo vaccine was administered within three months after the first screening HRA and six weeks after the second screening HRA, and subsequent vaccines two months ( $\pm 1$  week), and six months ( $\pm 2$  weeks) after first vaccination. Injections, 0.5 ml in the deltoid muscle, were generally given on the same side throughout the study.

|                                        |                                                                                                        |
|----------------------------------------|--------------------------------------------------------------------------------------------------------|
| Arm type                               | Active comparator                                                                                      |
| Investigational medicinal product name | qHPV L1 virus-like particle (VLP) vaccine (Gardasil-4®, Merck Sharp & Dohme (MSD), Kenilworth, NJ, USA |
| Investigational medicinal product code |                                                                                                        |
| Other name                             | Gardasil                                                                                               |
| Pharmaceutical forms                   | Injection                                                                                              |
| Routes of administration               | Intramuscular use                                                                                      |

Dosage and administration details:

qHPV L1 virus-like particle (VLP) vaccine (Gardasil-4®, Merck Sharp & Dohme (MSD), Kenilworth, NJ, USA) or a placebo (0.9% saline). The first qHPV or placebo vaccine was administered within three months after the first screening HRA and six weeks after the second screening HRA, and subsequent vaccines two months ( $\pm 1$  week), and six months ( $\pm 2$  weeks) after first vaccination. Injections, 0.5 ml in the deltoid muscle, were generally given on the same side throughout the study

|                                        |                   |
|----------------------------------------|-------------------|
| <b>Arm title</b>                       | placebo           |
| Arm description:<br>placebo injection  |                   |
| Arm type                               | Placebo           |
| Investigational medicinal product name | placebo           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

The first placebo vaccine was administered within three months after the first screening HRA and six weeks after the second screening HRA, and subsequent vaccines two months ( $\pm 1$  week), and six months ( $\pm 2$  weeks) after first vaccination. Injections, 0.5 ml in the deltoid muscle, were generally given on the same side throughout the study.

| <b>Number of subjects in period 1</b> | qHPV | placebo |
|---------------------------------------|------|---------|
| Started                               | 64   | 62      |
| Completed                             | 62   | 60      |
| Not completed                         | 2    | 2       |
| Lost to follow-up                     | 2    | 2       |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | qHPV    |
| Reporting group description:<br>qHPV L1 virus-like particle (VLP) vaccine (Gardasil-4®, Merck Sharp & Dohme (MSD), Kenilworth, NJ, USA) or a placebo (0.9% saline). The first qHPV or placebo vaccine was administered within three months after the first screening HRA and six weeks after the second screening HRA, and subsequent vaccines two months ( $\pm 1$ week), and six months ( $\pm 2$ weeks) after first vaccination. Injections, 0.5 ml in the deltoid muscle, were generally given on the same side throughout the study. |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | placebo |
| Reporting group description:<br>placebo injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |

| Reporting group values                             | qHPV | placebo | Total |
|----------------------------------------------------|------|---------|-------|
| Number of subjects                                 | 64   | 62      | 126   |
| Age categorical                                    |      |         |       |
| Units: Subjects                                    |      |         |       |
| In utero                                           | 0    | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0    | 0       | 0     |
| Newborns (0-27 days)                               | 0    | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0    | 0       | 0     |
| Children (2-11 years)                              | 0    | 0       | 0     |
| Adolescents (12-17 years)                          | 0    | 0       | 0     |
| Adults (18-64 years)                               | 63   | 57      | 120   |
| From 65-84 years                                   | 1    | 5       | 6     |
| 85 years and over                                  | 0    | 0       | 0     |
| Gender categorical                                 |      |         |       |
| Correctly enrolled and randomized                  |      |         |       |
| Units: Subjects                                    |      |         |       |
| Female                                             | 0    | 0       | 0     |
| Male                                               | 64   | 62      | 126   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | qHPV    |
| Reporting group description:<br>qHPV L1 virus-like particle (VLP) vaccine (Gardasil-4®, Merck Sharp & Dohme (MSD), Kenilworth, NJ, USA) or a placebo (0.9% saline). The first qHPV or placebo vaccine was administered within three months after the first screening HRA and six weeks after the second screening HRA, and subsequent vaccines two months ( $\pm 1$ week), and six months ( $\pm 2$ weeks) after first vaccination. Injections, 0.5 ml in the deltoid muscle, were generally given on the same side throughout the study. |         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | placebo |
| Reporting group description:<br>placebo injection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |

### Primary: Recurrences of HGAIN

|                                                                                                                                           |                      |
|-------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| End point title                                                                                                                           | Recurrences of HGAIN |
| End point description:<br>cumulative recurrence of biopsy-proven intra-anal or peri-anal HGAIN at 12 months after last vaccination (FU18) |                      |
| End point type                                                                                                                            | Primary              |
| End point timeframe:<br>12 months after last vaccination (FU18)                                                                           |                      |

| End point values            | qHPV            | placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 64              | 62              |  |  |
| Units: patients             |                 |                 |  |  |
| recurrences                 | 44              | 38              |  |  |

### Statistical analyses

|                                                    |                      |
|----------------------------------------------------|----------------------|
| Statistical analysis title                         | Prim endpoint        |
| Statistical analysis description:<br>Prim endpoint |                      |
| Comparison groups                                  | qHPV v placebo       |
| Number of subjects included in analysis            | 126                  |
| Analysis specification                             | Pre-specified        |
| Analysis type                                      | superiority          |
| P-value                                            | = 0.38               |
| Method                                             | Chi-squared          |
| Parameter estimate                                 | Risk difference (RD) |
| Point estimate                                     | -7.5                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -24.1   |
| upper limit         | 9.2     |

## Secondary: Occurrence of LGAIN

|                                                                                                     |                     |
|-----------------------------------------------------------------------------------------------------|---------------------|
| End point title                                                                                     | Occurrence of LGAIN |
| End point description:<br>cumulative occurrence of LGAIN at 12 months after last vaccination (FU18) |                     |
| End point type                                                                                      | Secondary           |
| End point timeframe:<br>12 months after last vaccination (FU18)                                     |                     |

| End point values            | qHPV            | placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 28              | 27              |  |  |
| Units: patients             |                 |                 |  |  |
| occurrence of LGAIN         | 21              | 18              |  |  |

## Statistical analyses

|                                         |                      |
|-----------------------------------------|----------------------|
| Statistical analysis title              | Sec endpoint LGAIN   |
| Comparison groups                       | placebo v qHPV       |
| Number of subjects included in analysis | 55                   |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | = 0.5                |
| Method                                  | Chi-squared          |
| Parameter estimate                      | Risk difference (RD) |
| Point estimate                          | -8.3                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -32.3                |
| upper limit                             | 15.6                 |

## Secondary: occurrence of anogenital condylomata

|                                                                                                                      |                                      |
|----------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| End point title                                                                                                      | occurrence of anogenital condylomata |
| End point description:<br>cumulative occurrence of anogenital condylomata at 12 months after last vaccination (FU18) |                                      |

|                                         |           |
|-----------------------------------------|-----------|
| End point type                          | Secondary |
| End point timeframe:                    |           |
| 12 months after last vaccination (FU18) |           |

| End point values            | qHPV            | placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 38              | 43              |  |  |
| Units: patients             |                 |                 |  |  |
| occurrence of warts         | 21              | 19              |  |  |

### Statistical analyses

| Statistical analysis title              | warts                |
|-----------------------------------------|----------------------|
| Comparison groups                       | qHPV v placebo       |
| Number of subjects included in analysis | 81                   |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | = 0.32               |
| Method                                  | Chi-squared          |
| Parameter estimate                      | Risk difference (RD) |
| Point estimate                          | -11.1                |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -32.8                |
| upper limit                             | 10.6                 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

first vaccination until 12 months after last vaccination

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | qHPV ITT |
|-----------------------|----------|

Reporting group description: -

|                       |             |
|-----------------------|-------------|
| Reporting group title | placebo ITT |
|-----------------------|-------------|

Reporting group description: -

| Serious adverse events                            | qHPV ITT                                                         | placebo ITT    |  |
|---------------------------------------------------|------------------------------------------------------------------|----------------|--|
| Total subjects affected by serious adverse events |                                                                  |                |  |
| subjects affected / exposed                       | 3 / 64 (4.69%)                                                   | 4 / 62 (6.45%) |  |
| number of deaths (all causes)                     | 0                                                                | 0              |  |
| number of deaths resulting from adverse events    | 0                                                                | 0              |  |
| Injury, poisoning and procedural complications    |                                                                  |                |  |
| Fracture                                          | Additional description: and accidents                            |                |  |
| subjects affected / exposed                       | 0 / 64 (0.00%)                                                   | 2 / 62 (3.23%) |  |
| occurrences causally related to treatment / all   | 0 / 0                                                            | 0 / 2          |  |
| deaths causally related to treatment / all        | 0 / 0                                                            | 0 / 0          |  |
| Cardiac disorders                                 |                                                                  |                |  |
| Myocardial infarction                             |                                                                  |                |  |
| subjects affected / exposed                       | 1 / 64 (1.56%)                                                   | 0 / 62 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1                                                            | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0                                                            | 0 / 0          |  |
| Hepatobiliary disorders                           |                                                                  |                |  |
| Hepatic encephalopathy                            |                                                                  |                |  |
| subjects affected / exposed                       | 0 / 64 (0.00%)                                                   | 1 / 62 (1.61%) |  |
| occurrences causally related to treatment / all   | 0 / 0                                                            | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0                                                            | 0 / 0          |  |
| Renal and urinary disorders                       |                                                                  |                |  |
| Nephrolithiasis                                   | Additional description: and renal insufficiency - by dehydration |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 64 (1.56%) | 1 / 62 (1.61%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Psychiatric decompensation                      |                |                |  |
| subjects affected / exposed                     | 1 / 64 (1.56%) | 0 / 62 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | qHPV ITT         | placebo ITT      |  |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 58 / 64 (90.63%) | 55 / 62 (88.71%) |  |
| Nervous system disorders                              |                  |                  |  |
| Nervous system disorder                               |                  |                  |  |
| subjects affected / exposed                           | 32 / 64 (50.00%) | 26 / 62 (41.94%) |  |
| occurrences (all)                                     | 32               | 26               |  |
| Gastrointestinal disorders                            |                  |                  |  |
| GI                                                    |                  |                  |  |
| subjects affected / exposed                           | 22 / 64 (34.38%) | 27 / 62 (43.55%) |  |
| occurrences (all)                                     | 22               | 27               |  |
| Respiratory, thoracic and mediastinal disorders       |                  |                  |  |
| Respiratory disorder                                  |                  |                  |  |
| subjects affected / exposed                           | 15 / 64 (23.44%) | 7 / 62 (11.29%)  |  |
| occurrences (all)                                     | 15               | 7                |  |
| Skin and subcutaneous tissue disorders                |                  |                  |  |
| Skin disorder                                         |                  |                  |  |
| subjects affected / exposed                           | 25 / 64 (39.06%) | 13 / 62 (20.97%) |  |
| occurrences (all)                                     | 25               | 13               |  |
| Musculoskeletal and connective tissue disorders       |                  |                  |  |
| Musculoskeletal disorder                              |                  |                  |  |
| subjects affected / exposed                           | 19 / 64 (29.69%) | 8 / 62 (12.90%)  |  |
| occurrences (all)                                     | 19               | 8                |  |
| Infections and infestations                           |                  |                  |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| Infection                   |                  |                  |  |
| subjects affected / exposed | 46 / 64 (71.88%) | 54 / 62 (87.10%) |  |
| occurrences (all)           | 46               | 54               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|      |
|------|
| none |
|------|

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33966029>