



## Clinical trial results:

**Human papillomavirus infection: a randomised controlled trial of Imiquimod cream (5%) versus Podophyllotoxin cream (0.15%), in combination with quadrivalent human papillomavirus or control vaccination in the treatment and prevention of recurrence of anogenital warts (HIPvac Trial).**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2013-002951-14  |
| Trial protocol           | GB              |
| Global end of trial date | 17 January 2018 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 24 October 2019 |
| First version publication date | 24 October 2019 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 12/0357 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |  |
|------------------------------------|--|
| ISRCTN number                      | ISRCTN32729817   |
| ClinicalTrials.gov id (NCT number) | -  |
| WHO universal trial number (UTN)   | -  |
| Other trial identifiers            | NIHR project number: 11/129/187, NIHR UKCRN identifier: 16857, IRAS identifier: 134697 |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Comprehensive Clinical Trials Unit at UCL   |
| Sponsor organisation address | Institute of Clinical Trials and Methodology, 90 High Holborn, London, United Kingdom, WC1V 6LJ |
| Public contact               | CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk          |
| Scientific contact           | CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk          |

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:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 19 March 2018   |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 17 January 2018 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 17 January 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To compare the effectiveness of imiquimod 5% cream versus podophyllotoxin 0.15% cream in the treatment of external anogenital warts. The primary objective was to compare the proportions of participants receiving each treatment who have complete resolution of warts by 16 weeks and remain free of warts up to 48 weeks after starting treatment. To compare the effectiveness of a course of quadrivalent HPV (qHPV) vaccine started at the same time as topical wart treatment with the placebo, in improving wart clearance at 16 weeks and preventing recurrence up to 48 weeks.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service Research Governance Framework for Health and Social Care. Dose and frequency modifications of topical treatment in the event of an adverse event were permitted. Podophyllotoxin (PDX): deferred for one week (three days of treatment), then restarted with twice-daily dosing (three days consecutively and four days off treatment, in weekly cycles); deferred for one week, then restarted with once-daily dosing; if PDX was not tolerated at any dose, then PDX stopped and either cryotherapy (4 weeks' post-randomisation) or imiquimod (after 16 weeks) given. Imiquimod (IMI): frequency of dosing reduced to twice a week; frequency of dosing reduced to once a week; if IMI was not tolerated at any dose, then IMI stopped and either cryotherapy (after 4 weeks) or PDX (after 16 weeks) given. Protocol pre-defined reasons for discontinuation of trial medication were in place in the event of participants experiencing: unacceptable treatment toxicity or adverse event; inter-current illness that prevents further treatment; withdrawal of consent for the treatment by the participant; pregnancy; suspected unexpected serious adverse reaction (SUSAR); any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment; protocol violations; cure; administrative reasons or other reasons. All participants could choose to discontinue trial treatment at any time, without giving a reason, without penalty or loss of benefits to which they would otherwise be entitled. Investigation and treatment of adverse events were as per NHS standard of care.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 17 November 2014 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 503 |
| Worldwide total number of subjects   | 503                 |
| EEA total number of subjects         | 503                 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 503 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited from 22 sexual health clinics in England and Wales with randomisations between 17 November 2014 and 06 January 2017. Participants were randomised (1:1) to IMIQ cream for up to 16 weeks or PDX cream for 4 weeks (up to 16 weeks), with simultaneous randomisation (1:1) to qHPV vaccine or saline control at 0, 8, 24 weeks.

### Pre-assignment

Screening details:

Adult patients presenting to genitourinary medicine clinics with first or repeat episode of external anogenital warts diagnosed clinically, untreated in the last 3 months, and no prior qHPV vaccine, who are suitable for self-administered topical wart treatment.

### 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:

Topical treatments were unblinded due to differences in posology, dispensed in original packs. The qHPV vaccine and saline placebo were dispensed as prefilled syringes in blinded packaging (opaque plastic sleeve inside a labelled carton). It was not possible to source matching syringes for a fully blinded placebo so the injection was administered by a member of staff who was not part of the trial team involved in the assessment of the participant.

### Arms

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

Arm description:

Application of 5% imiquimod (IMIQ) cream to wart area for three days of the week (every other day), for up to 16 weeks. Applied at bed time and left on overnight, then washed off after 6-10 hours + quadrivalent human papillomavirus vaccine (qHPV) administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Imiquimod         |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Cream             |
| Routes of administration               | Topical use       |

Dosage and administration details:

Application of 5% cream to wart area for three days of the week (every other day). The cream should be applied at bed time and left on overnight, then washed off after 6-10 hours.

|  |   |
|--|---|
| Investigational medicinal product name | Quadrivalent human papillomavirus vaccine [types 6, 11, 16, 18] |
| Investigational medicinal product code |   |
| Other name                             | Gardasil  |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe                  |
| Routes of administration               | Intramuscular use   |

Dosage and administration details:

Administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks); vaccine volume 0.5ml contains alum adjuvant.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | PDX + qHPV |
|------------------|------------|

**Arm description:**

Podophyllotoxin (PDX) 0.15% cream applied to the lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles + quadrivalent human papillomavirus vaccine (qHPV) administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Podophyllotoxin   |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Cream             |
| Routes of administration               | Topical use       |

**Dosage and administration details:**

Application of 0.15% Podophyllotoxin (PDX) cream to lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles. The licensed duration is 4 weeks, but it is common practice to extend this period if there is a partial response to therapy.

|  |   |
|--|---|
| Investigational medicinal product name | Quadrivalent human papillomavirus vaccine [types 6, 11, 16, 18] |
| Investigational medicinal product code |   |
| Other name                             | Gardasil  |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe                  |
| Routes of administration               | Intramuscular use   |

**Dosage and administration details:**

Administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks); vaccine volume 0.5ml, contains alum adjuvant.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | IMIQ + placebo |
|------------------|----------------|

**Arm description:**

Application of 5% Imiquimod (IMIQ) cream to wart area for three days of the week (every other day), for up to 16 weeks. Applied at bed time and left on overnight, then washed off after 6-10 hours + saline placebo administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Imiquimod         |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Cream             |
| Routes of administration               | Topical use       |

**Dosage and administration details:**

Application of 5% cream to wart area for three days of the week (every other day). The cream should be applied at bed time and left on overnight, then washed off after 6-10 hours.

|  |  |
|--|--|
| Investigational medicinal product name | Sodium chloride 0.9%                         |
| Investigational medicinal product code |  |
| Other name                             | Saline                                       |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Intramuscular use                            |

**Dosage and administration details:**

Administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks); volume 0.5ml.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | PDX + placebo |
|------------------|---------------|

**Arm description:**

Application of 0.15% Podophyllotoxin (PDX) cream to lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles + saline placebo administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Podophyllotoxin |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Cream           |
| Routes of administration               | Topical use     |

Dosage and administration details:

Application of 0.15% Podophyllotoxin (PDX) cream to lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles. The licensed duration is 4 weeks, but it is common practice to extend this period if there is a partial response to therapy.

|  |  |
|--|--|
| Investigational medicinal product name | Sodium chloride 0.9%                         |
| Investigational medicinal product code |  |
| Other name                             | Saline                                       |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Intramuscular use                            |

Dosage and administration details:

Administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks); volume 0.5ml.

| <b>Number of subjects in period 1</b> | IMIQ + qHPV | PDX + qHPV | IMIQ + placebo |
|---------------------------------------|-------------|------------|----------------|
| Started                               | 125         | 126        | 126            |
| Week 16                               | 105         | 106        | 103            |
| Week 48                               | 89          | 88         | 88             |
| Completed                             | 89          | 88         | 88             |
| Not completed                         | 36          | 38         | 38             |
| Lost to follow-up                     | 36          | 38         | 38             |

| <b>Number of subjects in period 1</b> | PDX + placebo |
|---------------------------------------|---------------|
| Started                               | 126           |
| Week 16                               | 103           |
| Week 48                               | 87            |
| Completed                             | 87            |
| Not completed                         | 39            |
| Lost to follow-up                     | 39            |

## Baseline characteristics

### Reporting groups

|  |                |
|--|----------------|
| Reporting group title  | IMIQ + qHPV    |
| Reporting group description:<br>Application of 5% imiquimod (IMIQ) cream to wart area for three days of the week (every other day), for up to 16 weeks. Applied at bed time and left on overnight, then washed off after 6-10 hours + quadrivalent human papillomavirus vaccine (qHPV) administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks). |                |
| Reporting group title  | PDX + qHPV     |
| Reporting group description:<br>Podophyllotoxin (PDX) 0.15% cream applied to the lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles + quadrivalent human papillomavirus vaccine (qHPV) administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).   |                |
| Reporting group title  | IMIQ + placebo |
| Reporting group description:<br>Application of 5% Imiquimod (IMIQ) cream to wart area for three days of the week (every other day), for up to 16 weeks. Applied at bed time and left on overnight, then washed off after 6-10 hours + saline placebo administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).                                   |                |
| Reporting group title  | PDX + placebo  |
| Reporting group description:<br>Application of 0.15% Podophyllotoxin (PDX) cream to lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles + saline placebo administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).  |                |

| Reporting group values                          | IMIQ + qHPV | PDX + qHPV | IMIQ + placebo |
|---|-------------|------------|----------------|
| Number of subjects                              | 125         | 126        | 126            |
| Age categorical<br>Units: Subjects              |             |            |                |
| Adults (18-64 years)                            |             |            |                |
| From 65-84 years                                |             |            |                |
| 85 years and over                               |             |            |                |
| Age continuous<br>Units: years                  |             |            |                |
| arithmetic mean                                 | 31          | 31         | 32             |
| standard deviation                              | ± 10        | ± 10       | ± 10           |
| Gender categorical<br>Units: Subjects           |             |            |                |
| Female  | 42          | 42         | 43             |
| Male  | 83          | 84         | 83             |
| Previous occurrence of warts<br>Units: Subjects |             |            |                |
| None  | 63          | 63         | 63             |
| 1 or more                                       | 62          | 63         | 63             |
| HIV positive<br>Units: Subjects                 |             |            |                |
| Yes   | 2           | 4          | 3              |
| No  | 123         | 122        | 123            |
| Total number of warts<br>Units: Subjects        |             |            |                |
| 1-5 warts                                       | 63          | 80         | 66             |

|  |     |     |     |
|--|-----|-----|-----|
| 6-10 warts   | 26  | 23  | 38  |
| 11-20 warts  | 24  | 15  | 17  |
| >20 warts  | 11  | 8   | 5   |
| Missing  | 1   | 0   | 0   |
| Sexual orientation<br>Units: Subjects  |     |     |     |
| Heterosexual   | 104 | 102 | 102 |
| Homosexual   | 15  | 20  | 16  |
| Bisexual   | 5   | 4   | 8   |
| Other  | 1   | 0   | 0   |
| Previous episode(s) of warts<br>Units: Subjects                                    |     |     |     |
| Yes  | 65  | 68  | 63  |
| No   | 60  | 58  | 63  |
| Previous treatment for warts (in those with a previous episode)<br>Units: Subjects |     |     |     |
| Yes  | 64  | 67  | 63  |
| No   | 1   | 1   | 0   |
| Not applicable   | 60  | 58  | 63  |
| Previous bivalent HPV vaccine<br>Units: Subjects                                   |     |     |     |
| Yes  | 10  | 12  | 8   |
| No   | 115 | 114 | 118 |
| Not recorded   | 0   | 0   | 0   |
| Smoking<br>Units: Subjects   |     |     |     |
| Daily  | 42  | 33  | 36  |
| Less than daily  | 13  | 15  | 10  |
| Ex-smoker  | 32  | 27  | 34  |
| Never smoked   | 37  | 50  | 46  |
| Missing  | 1   | 1   | 0   |
| Quality of Life reported<br>Units: Subjects  |     |     |     |
| Yes  | 110 | 116 | 119 |
| No   | 15  | 10  | 7   |
| Attended at least one follow-up visit<br>Units: Subjects                           |     |     |     |
| Yes  | 118 | 117 | 109 |
| No   | 7   | 9   | 17  |
| Switched topical treatment at any time<br>Units: Subjects                          |     |     |     |
| Yes  | 15  | 15  | 19  |
| No   | 110 | 111 | 107 |
| Timing of first topical treatment switch<br>Units: Subjects                        |     |     |     |
| Before 4 weeks   | 2   | 0   | 0   |
| 4-16 weeks   | 1   | 3   | 4   |
| After 16 weeks   | 12  | 12  | 15  |
| Not applicable   | 110 | 111 | 107 |
| Completed less than maximum licensed duration of topical treatment                 |     |     |     |



|   |     |     |     |
|---|-----|-----|-----|
| Units: Subjects   |     |     |     |
| Yes   | 71  | 13  | 68  |
| No  | 54  | 113 | 58  |
| Extended PDX beyond 4 weeks (PDX arms only)   |     |     |     |
| Units: Subjects   |     |     |     |
| Yes   | 0   | 87  | 0   |
| No  | 0   | 39  | 0   |
| Not applicable  | 125 | 0   | 126 |
| Any cryotherapy received  |     |     |     |
| Units: Subjects   |     |     |     |
| Yes   | 56  | 62  | 61  |
| No  | 69  | 64  | 65  |
| Timing of first cryotherapy   |     |     |     |
| Units: Subjects   |     |     |     |
| Before 4 weeks  | 0   | 1   | 1   |
| 4-16 weeks  | 17  | 24  | 9   |
| After 16 weeks  | 39  | 37  | 51  |
| Not applicable  | 69  | 64  | 65  |
| Received any other treatment at their treatment centre other than cryotherapy at any time |     |     |     |
| Units: Subjects   |     |     |     |
| Yes   | 5   | 4   | 4   |
| No  | 120 | 122 | 122 |
| Received any treatment from a source outside their treatment centre                       |     |     |     |
| Units: Subjects   |     |     |     |
| Yes   | 5   | 5   | 5   |
| No  | 120 | 121 | 121 |
| Number of vaccines given  |     |     |     |
| Units: Subjects   |     |     |     |
| None  | 1   | 0   | 0   |
| 1 dose  | 11  | 13  | 7   |
| 2 doses   | 17  | 15  | 11  |
| 3 doses   | 89  | 89  | 91  |
| Not recorded  | 7   | 9   | 17  |
| Reasons for withdrawal from topical treatment   |     |     |     |
| Units: Subjects   |     |     |     |
| Non-compliance  | 0   | 0   | 0   |
| Pregnancy   | 0   | 0   | 0   |
| Adverse reactions   | 6   | 1   | 2   |
| Lost to follow-up   | 19  | 19  | 21  |
| Other   | 1   | 4   | 1   |
| Not applicable  | 99  | 102 | 102 |
| Reasons for withdrawal from vaccine/placebo treatment                                     |     |     |     |
| Units: Subjects   |     |     |     |
| Pregnancy   | 0   | 0   | 0   |
| Adverse reactions   | 0   | 0   | 0   |
| Lost to follow-up   | 19  | 19  | 22  |
| Other   | 0   | 1   | 0   |

|                |     |     |     |
|----------------|-----|-----|-----|
| Not applicable | 106 | 106 | 104 |
|----------------|-----|-----|-----|

|   |                |                |                |
|---|----------------|----------------|----------------|
| Diameter of largest wart<br>Units: mm<br>median<br>inter-quartile range (Q1-Q3)   | 3<br>2 to 5    | 3<br>2 to 5    | 3<br>2 to 5    |
| Partners in the last 3 months<br>Units: Number of partners<br>median<br>inter-quartile range (Q1-Q3)                        | 1<br>1 to 1    | 1<br>1 to 2    | 1<br>1 to 1    |
| Number of qHPV doses administered<br>Units: Dose<br>median<br>inter-quartile range (Q1-Q3)                                  | 3<br>3 to 3    | 3<br>2 to 3    | 3<br>3 to 3    |
| Number of STI episodes<br>Units: episode<br>median<br>inter-quartile range (Q1-Q3)  | 0<br>0 to 1    | 0<br>0 to 1    | 0<br>0 to 1    |
| Quality of Life - EQ-5D-5L: Health Utility<br>Units: health utility<br>arithmetic mean<br>standard deviation                | 0.94<br>± 0.11 | 0.92<br>± 0.13 | 0.94<br>± 0.10 |
| Quality of Life - EQ-5D-5L: Visual analogue scale (VAS)<br>Units: score out of 100<br>arithmetic mean<br>standard deviation | 83<br>± 12     | 82<br>± 13     | 82<br>± 14     |

| Reporting group values  | PDX + placebo | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 126           | 503   |  |
| Age categorical<br>Units: Subjects                                      |               |       |  |
| Adults (18-64 years)  |               | 0     |  |
| From 65-84 years  |               | 0     |  |
| 85 years and over   |               | 0     |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 30<br>± 10    | -     |  |
| Gender categorical<br>Units: Subjects                                   |               |       |  |
| Female  | 43            | 170   |  |
| Male  | 83            | 333   |  |
| Previous occurrence of warts<br>Units: Subjects                         |               |       |  |
| None  | 63            | 252   |  |
| 1 or more   | 63            | 251   |  |
| HIV positive<br>Units: Subjects   |               |       |  |
| Yes   | 3             | 12    |  |
| No  | 123           | 491   |  |

|   |     |     |  |
|---|-----|-----|--|
| Total number of warts<br>Units: Subjects  |     |     |  |
| 1-5 warts   | 57  | 266 |  |
| 6-10 warts  | 32  | 119 |  |
| 11-20 warts   | 21  | 77  |  |
| >20 warts   | 16  | 40  |  |
| Missing   | 0   | 1   |  |
| Sexual orientation<br>Units: Subjects   |     |     |  |
| Heterosexual  | 102 | 410 |  |
| Homosexual  | 16  | 67  |  |
| Bisexual  | 8   | 25  |  |
| Other   | 0   | 1   |  |
| Previous episode(s) of warts<br>Units: Subjects                                       |     |     |  |
| Yes   | 64  | 260 |  |
| No  | 62  | 243 |  |
| Previous treatment for warts (in those<br>with a previous episode)<br>Units: Subjects |     |     |  |
| Yes   | 62  | 256 |  |
| No  | 2   | 4   |  |
| Not applicable  | 62  | 243 |  |
| Previous bivalent HPV vaccine<br>Units: Subjects                                      |     |     |  |
| Yes   | 13  | 43  |  |
| No  | 110 | 457 |  |
| Not recorded  | 3   | 3   |  |
| Smoking<br>Units: Subjects  |     |     |  |
| Daily   | 40  | 151 |  |
| Less than daily   | 21  | 59  |  |
| Ex-smoker   | 25  | 118 |  |
| Never smoked  | 40  | 173 |  |
| Missing   | 0   | 2   |  |
| Quality of Life reported<br>Units: Subjects   |     |     |  |
| Yes   | 110 | 455 |  |
| No  | 16  | 48  |  |
| Attended at least one follow-up visit<br>Units: Subjects                              |     |     |  |
| Yes   | 116 | 460 |  |
| No  | 10  | 43  |  |
| Switched topical treatment at any time<br>Units: Subjects                             |     |     |  |
| Yes   | 26  | 75  |  |
| No  | 100 | 428 |  |
| Timing of first topical treatment switch<br>Units: Subjects                           |     |     |  |
| Before 4 weeks  | 2   | 4   |  |
| 4-16 weeks  | 4   | 12  |  |

|  |     |     |  |
|--|-----|-----|--|
| After 16 weeks   | 20  | 59  |  |
| Not applicable   | 100 | 428 |  |
| Completed less than maximum licensed duration of topical treatment<br>Units: Subjects                        |     |     |  |
| Yes  | 16  | 168 |  |
| No   | 110 | 335 |  |
| Extended PDX beyond 4 weeks (PDX arms only)<br>Units: Subjects   |     |     |  |
| Yes  | 80  | 167 |  |
| No   | 46  | 85  |  |
| Not applicable   | 0   | 251 |  |
| Any cryotherapy received<br>Units: Subjects  |     |     |  |
| Yes  | 68  | 247 |  |
| No   | 58  | 256 |  |
| Timing of first cryotherapy<br>Units: Subjects   |     |     |  |
| Before 4 weeks   | 2   | 4   |  |
| 4-16 weeks   | 22  | 72  |  |
| After 16 weeks   | 44  | 171 |  |
| Not applicable   | 58  | 256 |  |
| Received any other treatment at their treatment centre other than cryotherapy at any time<br>Units: Subjects |     |     |  |
| Yes  | 9   | 22  |  |
| No   | 117 | 481 |  |
| Received any treatment from a source outside their treatment centre<br>Units: Subjects                       |     |     |  |
| Yes  | 6   | 21  |  |
| No   | 120 | 482 |  |
| Number of vaccines given<br>Units: Subjects  |     |     |  |
| None   | 0   | 1   |  |
| 1 dose   | 15  | 46  |  |
| 2 doses  | 13  | 56  |  |
| 3 doses  | 88  | 357 |  |
| Not recorded   | 10  | 43  |  |
| Reasons for withdrawal from topical treatment<br>Units: Subjects   |     |     |  |
| Non-compliance   | 1   | 1   |  |
| Pregnancy  | 1   | 1   |  |
| Adverse reactions  | 5   | 14  |  |
| Lost to follow-up  | 19  | 78  |  |
| Other  | 10  | 16  |  |
| Not applicable   | 90  | 393 |  |
| Reasons for withdrawal from vaccine/placebo treatment<br>Units: Subjects                                     |     |     |  |

|   |        |     |  |
|---|--------|-----|--|
| Pregnancy   | 1      | 1   |  |
| Adverse reactions                                       | 2      | 2   |  |
| Lost to follow-up                                       | 19     | 79  |  |
| Other   | 2      | 3   |  |
| Not applicable  | 102    | 418 |  |
| Diameter of largest wart                                |        |     |  |
| Units: mm   |        |     |  |
| median  | 3      |     |  |
| inter-quartile range (Q1-Q3)                            | 2 to 5 | -   |  |
| Partners in the last 3 months                           |        |     |  |
| Units: Number of partners                               |        |     |  |
| median  | 1      |     |  |
| inter-quartile range (Q1-Q3)                            | 1 to 1 | -   |  |
| Number of qHPV doses administered                       |        |     |  |
| Units: Dose   |        |     |  |
| median  | 3      |     |  |
| inter-quartile range (Q1-Q3)                            | 3 to 3 | -   |  |
| Number of STI episodes                                  |        |     |  |
| Units: episode  |        |     |  |
| median  | 0      |     |  |
| inter-quartile range (Q1-Q3)                            | 0 to 1 | -   |  |
| Quality of Life - EQ-5D-5L: Health Utility              |        |     |  |
| Units: health utility                                   |        |     |  |
| arithmetic mean   | 0.92   |     |  |
| standard deviation                                      | ± 0.10 | -   |  |
| Quality of Life - EQ-5D-5L: Visual analogue scale (VAS) |        |     |  |
| Units: score out of 100                                 |        |     |  |
| arithmetic mean   | 82     |     |  |
| standard deviation                                      | ± 15   | -   |  |

## End points

### End points reporting groups

|  |                             |
|--|-----------------------------|
| Reporting group title  | IMIQ + qHPV                 |
| Reporting group description:<br>Application of 5% imiquimod (IMIQ) cream to wart area for three days of the week (every other day), for up to 16 weeks. Applied at bed time and left on overnight, then washed off after 6-10 hours + quadrivalent human papillomavirus vaccine (qHPV) administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks). |                             |
| Reporting group title  | PDX + qHPV                  |
| Reporting group description:<br>Podophyllotoxin (PDX) 0.15% cream applied to the lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles + quadrivalent human papillomavirus vaccine (qHPV) administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).   |                             |
| Reporting group title  | IMIQ + placebo              |
| Reporting group description:<br>Application of 5% Imiquimod (IMIQ) cream to wart area for three days of the week (every other day), for up to 16 weeks. Applied at bed time and left on overnight, then washed off after 6-10 hours + saline placebo administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).                                   |                             |
| Reporting group title  | PDX + placebo               |
| Reporting group description:<br>Application of 0.15% Podophyllotoxin (PDX) cream to lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles + saline placebo administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks).  |                             |
| Subject analysis set title   | IMIQ                        |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:<br>This reporting group were randomised to receive Imiquimod, whether in combination with qHPV vaccine or placebo. Therefore, the included arms are IMIQ + qHPV and IMIQ + placebo.  |                             |
| Subject analysis set title   | PDX                         |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:<br>This reporting group were randomised to receive PDX, whether in combination with qHPV or placebo. Therefore, the included arms are PDX + qHPV and PDX + placebo.  |                             |
| Subject analysis set title   | qHPV                        |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:<br>This reporting group were randomised to receive qHPV vaccine, whether in combination with IMIQ or PDX topical treatment. Therefore, the included arms are IMIQ + qHPV and PDX + qHPV.   |                             |
| Subject analysis set title   | Placebo                     |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:<br>This reporting group were randomised to receive placebo vaccine, whether in combination with IMIQ or PDX. Therefore, the included arms are IMIQ + placebo and PDX + placebo.  |                             |

### Primary: Wart free at 16 weeks and remaining wart free between 16 and 48 weeks - Topical effect

|  |  |
|--|--|
| End point title  | Wart free at 16 weeks and remaining wart free between 16 and 48 weeks - Topical effect |
| End point description:<br>Proportion of participants who were wart free by 16 weeks, and who remained wart free to 48 weeks (no recurrences) |  |
| End point type   | Primary  |
| End point timeframe:<br>Assessed from 16 to 48 weeks post-randomisation.   |  |

| <b>End point values</b>     | IMIQ + qHPV     | PDX + qHPV      | IMIQ + placebo  | PDX + placebo   |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 101             | 99              | 98              | 99              |
| Units: participants         |                 |                 |                 |                 |
| Achieved                    | 35              | 38              | 25              | 30              |
| Not achieved                | 66              | 61              | 73              | 69              |

| <b>End point values</b>     | IMIQ                 | PDX                  |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 199                  | 198                  |  |  |
| Units: participants         |                      |                      |  |  |
| Achieved                    | 60                   | 68                   |  |  |
| Not achieved                | 139                  | 130                  |  |  |

## Statistical analyses

| <b>Statistical analysis title</b> | Primary analysis |
|-----------------------------------|------------------|
|-----------------------------------|------------------|

Statistical analysis description:

Analysis carried out on multiply imputed data.

The analysis for the trial treatment factors (vaccine and topical) are based on comparisons at the margins of the 2 x 2 table, meaning all participants randomised to PDX will be compared with all participants randomised to IMIQ, and all participants randomised to qHPV vaccine will be compared with all participants randomised to saline placebo.

|   |                            |
|---|----------------------------|
| Comparison groups                       | IMIQ v PDX                 |
| Number of subjects included in analysis | 397                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | > 0.05                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 0.81                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.54                       |
| upper limit                             | 1.23                       |

Notes:

[1] - Reference group - PDX

| <b>Statistical analysis title</b> | Complete case analysis |
|-----------------------------------|------------------------|
| Comparison groups                 | IMIQ v PDX             |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 397                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | > 0.05                |
| Method                                  | Mixed models analysis |
| Parameter estimate                      | Odds ratio (OR)       |
| Point estimate                          | 0.82                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.53                  |
| upper limit                             | 1.27                  |

### Primary: Wart free at 16 weeks and remaining wart free between 16 and 48 weeks - Vaccine effect

|                        |  |
|------------------------|--|
| End point title        | Wart free at 16 weeks and remaining wart free between 16 and 48 weeks - Vaccine effect             |
| End point description: | Proportion of participants who were wart free by 16 weeks, and who remained wart free to 48 weeks. |
| End point type         | Primary  |
| End point timeframe:   | Assessed from 16 to 48 weeks post-randomisation  |

| End point values            | IMIQ + qHPV     | PDX + qHPV      | IMIQ + placebo  | PDX + placebo   |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 101             | 99              | 98              | 99              |
| Units: Subjects             |                 |                 |                 |                 |
| Achieved                    | 35              | 38              | 25              | 30              |
| Not achieved                | 66              | 61              | 73              | 69              |

| End point values            | qHPV                 | Placebo              |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 200                  | 197                  |  |  |
| Units: Subjects             |                      |                      |  |  |
| Achieved                    | 73                   | 55                   |  |  |
| Not achieved                | 127                  | 142                  |  |  |

### Statistical analyses

|                            |                  |
|----------------------------|------------------|
| Statistical analysis title | Primary analysis |
|----------------------------|------------------|



---

**Statistical analysis description:**

Analysis carried out on multiply imputed data.

The analysis for the trial treatment factors (vaccine and topical) are based on comparisons at the margins of the 2 x 2 table, meaning all participants randomised to PDX will be compared with all participants randomised to IMIQ, and all participants randomised to qHPV vaccine will be compared with all participants randomised to saline placebo.

|   |                            |
|---|----------------------------|
| Comparison groups                       | qHPV v Placebo             |
| Number of subjects included in analysis | 397                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| P-value                                 | > 0.05                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 1.46                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.97                       |
| upper limit                             | 2.2                        |

Notes:

[2] - Reference group - Placebo

|   |                        |
|---|------------------------|
| <b>Statistical analysis title</b>       | Complete case analysis |
| Comparison groups                       | qHPV v Placebo         |
| Number of subjects included in analysis | 397                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | ≥ 0.05                 |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Odds ratio (OR)        |
| Point estimate                          | 1.55                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 1                      |
| upper limit                             | 2.41                   |

---

**Secondary: Remaining wart free at 48 weeks after clearance at 16 weeks - Vaccine effect**

|                        |  |
|------------------------|--|
| End point title        | Remaining wart free at 48 weeks after clearance at 16 weeks - Vaccine effect |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Assessed up to Week 48 |  |

| End point values            | IMIQ + qHPV     | PDX + qHPV      | IMIQ + placebo  | PDX + placebo   |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43              | 53              | 39              | 42              |
| Units: Subjects             |                 |                 |                 |                 |
| Achieved                    | 35              | 38              | 25              | 30              |
| Not achieved                | 9               | 15              | 14              | 12              |

| End point values            | qHPV                 | Placebo              |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 96                   | 81                   |  |  |
| Units: Subjects             |                      |                      |  |  |
| Achieved                    | 73                   | 55                   |  |  |
| Not achieved                | 23                   | 26                   |  |  |

## Statistical analyses

| Statistical analysis title              | Primary analysis           |
|---|----------------------------|
| Comparison groups                       | qHPV v Placebo             |
| Number of subjects included in analysis | 177                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | > 0.05                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 1.39                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.73                       |
| upper limit                             | 2.63                       |

Notes:

[3] - Analysis carried out on multiply imputed data.

The analysis for the trial treatment factors (vaccine and topical) are based on comparisons at the margins of the 2 x 2 table, meaning all participants randomised to PDX will be compared with all participants randomised to IMIQ, and all participants randomised to qHPV vaccine will be compared with all participants randomised to saline placebo.

| Statistical analysis title              | Complete case analysis |
|---|------------------------|
| Comparison groups                       | qHPV v Placebo         |
| Number of subjects included in analysis | 177                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | > 0.05                 |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Odds ratio (OR)        |
| Point estimate                          | 1.8                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.9     |
| upper limit         | 3.63    |

### Secondary: Remaining wart free at 48 weeks after clearance at 16 weeks - Topical effect

|                        |  |
|------------------------|--|
| End point title        | Remaining wart free at 48 weeks after clearance at 16 weeks - Topical effect |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Assessed at 48 weeks   |  |

| End point values            | IMIQ + qHPV     | PDX + qHPV      | IMIQ + placebo  | PDX + placebo   |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43              | 53              | 39              | 42              |
| Units: Subjects             |                 |                 |                 |                 |
| Achieved                    | 35              | 38              | 25              | 30              |
| Not achieved                | 9               | 15              | 14              | 12              |

| End point values            | IMIQ                 | PDX                  |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 82                   | 95                   |  |  |
| Units: Subjects             |                      |                      |  |  |
| Achieved                    | 60                   | 68                   |  |  |
| Not achieved                | 22                   | 27                   |  |  |

### Statistical analyses

|   |                            |
|---|----------------------------|
| Statistical analysis title              | Primary analysis           |
| Comparison groups                       | IMIQ v PDX                 |
| Number of subjects included in analysis | 177                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[4]</sup> |
| P-value                                 | > 0.05                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 0.98                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.54    |
| upper limit         | 1.78    |

Notes:

[4] - Reference group - PDX

|   |                        |
|---|------------------------|
| <b>Statistical analysis title</b>       | Complete case analysis |
| Comparison groups                       | IMIQ v PDX             |
| Number of subjects included in analysis | 177                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | > 0.05                 |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Odds ratio (OR)        |
| Point estimate                          | 0.97                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.48                   |
| upper limit                             | 1.95                   |

### Secondary: Wart free at 16 weeks - Topical effect

|                        |  |
|------------------------|--|
| End point title        | Wart free at 16 weeks - Topical effect |
| End point description: |  |
| End point type         | Secondary                              |
| End point timeframe:   |  |
| Assessed at 16 weeks   |  |

| End point values            | IMIQ + qHPV     | PDX + qHPV      | IMIQ + placebo  | PDX + placebo   |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 104             | 105             | 103             | 102             |
| Units: Subjects             |                 |                 |                 |                 |
| Achieved                    | 58              | 70              | 56              | 57              |
| Not achieved                | 46              | 35              | 47              | 45              |

| End point values            | IMIQ                 | PDX                  |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 207                  | 207                  |  |  |
| Units: Subjects             |                      |                      |  |  |

|              |     |     |  |  |
|--------------|-----|-----|--|--|
| Achieved     | 114 | 127 |  |  |
| Not achieved | 93  | 80  |  |  |

## Statistical analyses

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Primary analysis           |
| Comparison groups                       | IMIQ v PDX                 |
| Number of subjects included in analysis | 414                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[5]</sup> |
| P-value                                 | > 0.05                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 0.77                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.52                       |
| upper limit                             | 1.14                       |

Notes:

[5] - Reference group - PDX

|   |                        |
|---|------------------------|
| <b>Statistical analysis title</b>       | Complete case analysis |
| Comparison groups                       | IMIQ v PDX             |
| Number of subjects included in analysis | 414                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | > 0.05                 |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Odds ratio (OR)        |
| Point estimate                          | 0.76                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.51                   |
| upper limit                             | 1.13                   |

## Secondary: Wart free at 16 weeks - Vaccine effect

|                        |  |
|------------------------|--|
| End point title        | Wart free at 16 weeks - Vaccine effect |
| End point description: |  |
| End point type         | Secondary                              |
| End point timeframe:   |  |
| Assessed at 16 weeks   |  |

| <b>End point values</b>     | IMIQ + qHPV     | PDX + qHPV      | IMIQ + placebo  | PDX + placebo   |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 104             | 105             | 103             | 102             |
| Units: Subjects             |                 |                 |                 |                 |
| Achieved                    | 58              | 70              | 56              | 57              |
| Not achieved                | 46              | 35              | 47              | 45              |

| <b>End point values</b>     | qHPV                 | Placebo              |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 209                  | 205                  |  |  |
| Units: Subjects             |                      |                      |  |  |
| Achieved                    | 128                  | 113                  |  |  |
| Not achieved                | 81                   | 92                   |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Primary analysis           |
|---|----------------------------|
| Comparison groups                       | qHPV v Placebo             |
| Number of subjects included in analysis | 414                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[6]</sup> |
| P-value                                 | > 0.05                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 1.3                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.89                       |
| upper limit                             | 1.91                       |

Notes:

[6] - Reference group - Placebo

| <b>Statistical analysis title</b>       | Complete case analysis |
|---|------------------------|
| Comparison groups                       | qHPV v Placebo         |
| Number of subjects included in analysis | 414                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | > 0.05                 |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Odds ratio (OR)        |
| Point estimate                          | 1.31                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.88    |
| upper limit         | 1.95    |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Non-serious adverse events (AEs) and adverse reactions (ARs) within 5 working days to the Sponsor (UCL CCTU). Serious AEs and serious ARs should be reported immediately to the Sponsor.

Adverse event reporting additional description:

Do not include:

- Local reactions to topical treatment/vaccinations
- Medical or surgical procedures
- Pre-existing disease/condition present before treatment that does not worsen
- Hospitalisation where no untoward/unintended response has occurred
- Medication overdose without signs/symptoms
- Complications of standard therapy
- Elective abortions

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

### Dictionary used

|                    |       |
|--------------------|-------|
| Dictionary name    | CTCAE |
| Dictionary version | 4.0   |

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Podophyllotoxin (PDX) |
|-----------------------|-----------------------|

Reporting group description:

Podophyllotoxin 0.15% cream applied to the lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles. The licensed treatment duration is 4 weeks, but it is common practice to extend this period if there is a partial response to therapy.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Imiquimod (IMIQ) |
|-----------------------|------------------|

Reporting group description:

Application of 5% cream to wart area for three days of the week (every other day), for up to 16 weeks. Applied at bed time and left on overnight, then washed off after 6-10 hours.

|                       |  |
|-----------------------|--|
| Reporting group title | Quadrivalent human papillomavirus vaccine (qHPV) |
|-----------------------|--|

Reporting group description:

Administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks); vaccine volume 0.5ml; contains alum adjuvant.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Saline (placebo) |
|-----------------------|------------------|

Reporting group description:

Administered at 0, 2, and 6 months (baseline, 8 weeks, 24 weeks); vaccine volume 0.5ml.

| Serious adverse events                            | Podophyllotoxin (PDX) | Imiquimod (IMIQ) | Quadrivalent human papillomavirus vaccine (qHPV) |
|---|-----------------------|------------------|--|
| Total subjects affected by serious adverse events |                       |                  |  |
| subjects affected / exposed                       | 10 / 252 (3.97%)      | 7 / 251 (2.79%)  | 9 / 251 (3.59%)                                  |
| number of deaths (all causes)                     | 0                     | 0                | 0  |
| number of deaths resulting from adverse events    | 0                     | 0                | 0  |
| Surgical and medical procedures                   |                       |                  |  |
| Myomectomy  |                       |                  |  |
| subjects affected / exposed                       | 0 / 252 (0.00%)       | 1 / 251 (0.40%)  | 1 / 251 (0.40%)                                  |
| occurrences causally related to treatment / all   | 0 / 0                 | 0 / 1            | 0 / 1  |
| deaths causally related to treatment / all        | 0 / 0                 | 0 / 0            | 0 / 0  |



|   |   |                 |                 |
|---|---|-----------------|-----------------|
| Pregnancy, puerperium and perinatal conditions  |   |                 |                 |
| Foetal death                                    | Additional description: Miscarriage at 20 weeks (fetal death), grade 3. |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)   | 1 / 251 (0.40%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Pregnancy                                       |   |                 |                 |
| subjects affected / exposed                     | 2 / 252 (0.79%)   | 0 / 251 (0.00%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |   |                 |                 |
| Uterine infection                               | Additional description: Grade 3.  |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)   | 1 / 251 (0.40%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Rupture of infected uterine fibroid             |   |                 |                 |
| alternative assessment type: Non-systematic     |   |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)   | 1 / 251 (0.40%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |   |                 |                 |
| Pneumothorax                                    |   |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)   | 1 / 251 (0.40%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Product issues                                  |   |                 |                 |
| Psychosis                                       |   |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)   | 1 / 251 (0.40%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |   |                 |                 |
| Motorcycle accident                             |   |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 252 (0.40%) | 0 / 251 (0.00%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Pericarditis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 252 (0.40%) | 0 / 251 (0.00%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Occipital neuralgia                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 252 (0.40%) | 0 / 251 (0.00%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Lymphadenopathy                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 252 (0.40%) | 0 / 251 (0.00%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%) | 1 / 251 (0.40%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal pain                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 252 (0.40%) | 0 / 251 (0.00%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coeliac disease                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 252 (0.40%) | 0 / 251 (0.00%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal pain                                  |                 |                 |                 |

|   |                                  |                 |                 |
|---|----------------------------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 252 (0.40%)                  | 0 / 251 (0.00%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1                            | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                            | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                                  |                 |                 |
| Skin ulceration                                 | Additional description: Grade 3. |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)                  | 1 / 251 (0.40%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0                            | 1 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                            | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                                  |                 |                 |
| Urinary retention                               |                                  |                 |                 |
| subjects affected / exposed                     | 1 / 252 (0.40%)                  | 0 / 251 (0.00%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1                            | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                            | 0 / 0           | 0 / 0           |
| Endocrine disorders                             |                                  |                 |                 |
| Thyrotoxicosis                                  |                                  |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)                  | 1 / 251 (0.40%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                            | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                            | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                                  |                 |                 |
| Sepsis  |                                  |                 |                 |
| subjects affected / exposed                     | 1 / 252 (0.40%)                  | 0 / 251 (0.00%) | 1 / 251 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1                            | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                            | 0 / 0           | 0 / 0           |
| Chest infection                                 |                                  |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)                  | 1 / 251 (0.40%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                            | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                            | 0 / 0           | 0 / 0           |
| Ear infection                                   |                                  |                 |                 |
| subjects affected / exposed                     | 0 / 252 (0.00%)                  | 1 / 251 (0.40%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                            | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                            | 0 / 0           | 0 / 0           |
| Anorectal infection                             |                                  |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 252 (0.40%) | 0 / 251 (0.00%) | 0 / 251 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |   |  |  |
|---|---|--|--|
| <b>Serious adverse events</b>                     | Saline (placebo)  |  |  |
| Total subjects affected by serious adverse events |   |  |  |
| subjects affected / exposed                       | 8 / 252 (3.17%)   |  |  |
| number of deaths (all causes)                     | 0   |  |  |
| number of deaths resulting from adverse events    | 0   |  |  |
| Surgical and medical procedures                   |   |  |  |
| Myomectomy  |   |  |  |
| subjects affected / exposed                       | 0 / 252 (0.00%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 0   |  |  |
| deaths causally related to treatment / all        | 0 / 0   |  |  |
| Pregnancy, puerperium and perinatal conditions    |   |  |  |
| Foetal death                                      | Additional description: Miscarriage at 20 weeks (fetal death), grade 3. |  |  |
| subjects affected / exposed                       | 0 / 252 (0.00%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 0   |  |  |
| deaths causally related to treatment / all        | 0 / 0   |  |  |
| Pregnancy   |   |  |  |
| subjects affected / exposed                       | 1 / 252 (0.40%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1   |  |  |
| deaths causally related to treatment / all        | 0 / 0   |  |  |
| Reproductive system and breast disorders          |   |  |  |
| Uterine infection                                 | Additional description: Grade 3.  |  |  |
| subjects affected / exposed                       | 0 / 252 (0.00%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 0   |  |  |
| deaths causally related to treatment / all        | 0 / 0   |  |  |
| Rupture of infected uterine fibroid               |   |  |  |
| alternative assessment type: Non-systematic       |   |  |  |
| subjects affected / exposed                       | 0 / 252 (0.00%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 0   |  |  |
| deaths causally related to treatment / all        | 0 / 0   |  |  |
| Respiratory, thoracic and mediastinal disorders   |   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Pneumothorax                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 252 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Product issues                                  |                 |  |  |
| Psychosis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 252 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Motorcycle accident                             |                 |  |  |
| subjects affected / exposed                     | 0 / 252 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Pericarditis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 252 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Occipital neuralgia                             |                 |  |  |
| subjects affected / exposed                     | 0 / 252 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Lymphadenopathy                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 252 (0.40%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Diarrhoea                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 252 (0.40%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal pain                           |                 |  |  |

|   |                                  |  |  |
|---|----------------------------------|--|--|
| subjects affected / exposed                     | 1 / 252 (0.40%)                  |  |  |
| occurrences causally related to treatment / all | 0 / 1                            |  |  |
| deaths causally related to treatment / all      | 0 / 0                            |  |  |
| Coeliac disease                                 |                                  |  |  |
| subjects affected / exposed                     | 1 / 252 (0.40%)                  |  |  |
| occurrences causally related to treatment / all | 0 / 1                            |  |  |
| deaths causally related to treatment / all      | 0 / 0                            |  |  |
| Abdominal pain                                  |                                  |  |  |
| subjects affected / exposed                     | 1 / 252 (0.40%)                  |  |  |
| occurrences causally related to treatment / all | 0 / 1                            |  |  |
| deaths causally related to treatment / all      | 0 / 0                            |  |  |
| Skin and subcutaneous tissue disorders          |                                  |  |  |
| Skin ulceration                                 | Additional description: Grade 3. |  |  |
| subjects affected / exposed                     | 0 / 252 (0.00%)                  |  |  |
| occurrences causally related to treatment / all | 0 / 0                            |  |  |
| deaths causally related to treatment / all      | 0 / 0                            |  |  |
| Renal and urinary disorders                     |                                  |  |  |
| Urinary retention                               |                                  |  |  |
| subjects affected / exposed                     | 1 / 252 (0.40%)                  |  |  |
| occurrences causally related to treatment / all | 0 / 1                            |  |  |
| deaths causally related to treatment / all      | 0 / 0                            |  |  |
| Endocrine disorders                             |                                  |  |  |
| Thyrotoxicosis                                  |                                  |  |  |
| subjects affected / exposed                     | 1 / 252 (0.40%)                  |  |  |
| occurrences causally related to treatment / all | 0 / 1                            |  |  |
| deaths causally related to treatment / all      | 0 / 0                            |  |  |
| Infections and infestations                     |                                  |  |  |
| Sepsis  |                                  |  |  |
| subjects affected / exposed                     | 0 / 252 (0.00%)                  |  |  |
| occurrences causally related to treatment / all | 0 / 0                            |  |  |
| deaths causally related to treatment / all      | 0 / 0                            |  |  |
| Chest infection                                 |                                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 252 (0.40%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear infection                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 252 (0.40%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anorectal infection                             |                 |  |  |
| subjects affected / exposed                     | 1 / 252 (0.40%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Podophyllotoxin (PDX) | Imiquimod (IMI)    | Quadrivalent human papillomavirus vaccine (qHPV) |
|---|-----------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                       |                    |  |
| subjects affected / exposed                           | 102 / 252 (40.48%)    | 131 / 251 (52.19%) | 112 / 251 (44.62%)                               |
| Vascular disorders                                    |                       |                    |  |
| Various vascular                                      |                       |                    |  |
| subjects affected / exposed                           | 1 / 252 (0.40%)       | 0 / 251 (0.00%)    | 1 / 251 (0.40%)                                  |
| occurrences (all)                                     | 1                     | 0                  | 1  |
| General disorders and administration site conditions  |                       |                    |  |
| Various general                                       |                       |                    |  |
| subjects affected / exposed                           | 6 / 252 (2.38%)       | 16 / 251 (6.37%)   | 10 / 251 (3.98%)                                 |
| occurrences (all)                                     | 6                     | 16                 | 10   |
| Reproductive system and breast disorders              |                       |                    |  |
| Various reproductive & breast                         |                       |                    |  |
| subjects affected / exposed                           | 2 / 252 (0.79%)       | 2 / 251 (0.80%)    | 2 / 251 (0.80%)                                  |
| occurrences (all)                                     | 2                     | 2                  | 2  |
| Respiratory, thoracic and mediastinal disorders       |                       |                    |  |
| Various respiratory, thoracic                         |                       |                    |  |
| subjects affected / exposed                           | 6 / 252 (2.38%)       | 5 / 251 (1.99%)    | 4 / 251 (1.59%)                                  |
| occurrences (all)                                     | 6                     | 5                  | 4  |
| Psychiatric disorders                                 |                       |                    |  |

|   |                      |                        |                      |
|---|----------------------|------------------------|----------------------|
| Various psychiatric subjects affected / exposed occurrences (all)   | 6 / 252 (2.38%)<br>6 | 0 / 251 (0.00%)<br>0   | 5 / 251 (1.99%)<br>5 |
| Investigations<br>Various investigations subjects affected / exposed occurrences (all)                            | 1 / 252 (0.40%)<br>1 | 1 / 251 (0.40%)<br>1   | 1 / 251 (0.40%)<br>1 |
| Injury, poisoning and procedural complications<br>Various injury subjects affected / exposed occurrences (all)    | 5 / 252 (1.98%)<br>5 | 7 / 251 (2.79%)<br>7   | 3 / 251 (1.20%)<br>3 |
| Cardiac disorders<br>Various cardiac subjects affected / exposed occurrences (all)                                | 1 / 252 (0.40%)<br>1 | 0 / 251 (0.00%)<br>0   | 1 / 251 (0.40%)<br>1 |
| Nervous system disorders<br>Various nervous system subjects affected / exposed occurrences (all)                  | 7 / 252 (2.78%)<br>7 | 5 / 251 (1.99%)<br>5   | 6 / 251 (2.39%)<br>6 |
| Blood and lymphatic system disorders<br>Various blood and lymphatic subjects affected / exposed occurrences (all) | 3 / 252 (1.19%)<br>3 | 1 / 251 (0.40%)<br>1   | 3 / 251 (1.20%)<br>3 |
| Ear and labyrinth disorders<br>Various ear and labyrinth subjects affected / exposed occurrences (all)            | 2 / 252 (0.79%)<br>2 | 0 / 251 (0.00%)<br>0   | 1 / 251 (0.40%)<br>1 |
| Eye disorders<br>Various eye subjects affected / exposed occurrences (all)  | 3 / 252 (1.19%)<br>3 | 0 / 251 (0.00%)<br>0   | 2 / 251 (0.80%)<br>2 |
| Gastrointestinal disorders<br>Various GI subjects affected / exposed occurrences (all)                            | 8 / 252 (3.17%)<br>8 | 10 / 251 (3.98%)<br>10 | 5 / 251 (1.99%)<br>5 |
| Skin and subcutaneous tissue disorders<br>Various skin  |                      |                        |                      |



|  |                        |                         |                         |
|--|------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)   | 23 / 252 (9.13%)<br>23 | 45 / 251 (17.93%)<br>45 | 29 / 251 (11.55%)<br>29 |
| Renal and urinary disorders<br>Various renal & urinary<br>subjects affected / exposed<br>occurrences (all)               | 1 / 252 (0.40%)<br>1   | 0 / 251 (0.00%)<br>0    | 0 / 251 (0.00%)<br>0    |
| Musculoskeletal and connective tissue disorders<br>Various MSK<br>subjects affected / exposed<br>occurrences (all)       | 3 / 252 (1.19%)<br>3   | 7 / 251 (2.79%)<br>7    | 6 / 251 (2.39%)<br>6    |
| Infections and infestations<br>Various infections<br>subjects affected / exposed<br>occurrences (all)                    | 23 / 252 (9.13%)<br>23 | 28 / 251 (11.16%)<br>28 | 29 / 251 (11.55%)<br>29 |
| Metabolism and nutrition disorders<br>Various metabolism & nutrition<br>subjects affected / exposed<br>occurrences (all) | 1 / 252 (0.40%)<br>1   | 2 / 251 (0.80%)<br>2    | 2 / 251 (0.80%)<br>2    |

|   |                        |  |  |
|---|------------------------|--|--|
| <b>Non-serious adverse events</b>   | Saline (placebo)       |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 121 / 252 (48.02%)     |  |  |
| Vascular disorders<br>Various vascular<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 252 (0.00%)<br>0   |  |  |
| General disorders and administration site conditions<br>Various general<br>subjects affected / exposed<br>occurrences (all)   | 12 / 252 (4.76%)<br>12 |  |  |
| Reproductive system and breast disorders<br>Various reproductive & breast<br>subjects affected / exposed<br>occurrences (all) | 2 / 252 (0.79%)<br>2   |  |  |
| Respiratory, thoracic and mediastinal disorders   |                        |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Various respiratory, thoracic subjects affected / exposed occurrences (all)                                       | 7 / 252 (2.78%)<br>7 |  |  |
| Psychiatric disorders<br>Various psychiatric subjects affected / exposed occurrences (all)                        | 1 / 252 (0.40%)<br>1 |  |  |
| Investigations<br>Various investigations subjects affected / exposed occurrences (all)                            | 1 / 252 (0.40%)<br>1 |  |  |
| Injury, poisoning and procedural complications<br>Various injury subjects affected / exposed occurrences (all)    | 9 / 252 (3.57%)<br>9 |  |  |
| Cardiac disorders<br>Various cardiac subjects affected / exposed occurrences (all)                                | 0 / 252 (0.00%)<br>0 |  |  |
| Nervous system disorders<br>Various nervous system subjects affected / exposed occurrences (all)                  | 6 / 252 (2.38%)<br>6 |  |  |
| Blood and lymphatic system disorders<br>Various blood and lymphatic subjects affected / exposed occurrences (all) | 1 / 252 (0.40%)<br>1 |  |  |
| Ear and labyrinth disorders<br>Various ear and labyrinth subjects affected / exposed occurrences (all)            | 1 / 252 (0.40%)<br>1 |  |  |
| Eye disorders<br>Various eye subjects affected / exposed occurrences (all)  | 1 / 252 (0.40%)<br>1 |  |  |
| Gastrointestinal disorders<br>Various GI  |                      |  |  |

|  |                         |  |  |
|--|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 13 / 252 (5.16%)<br>13  |  |  |
| Skin and subcutaneous tissue disorders<br>Various skin<br>subjects affected / exposed<br>occurrences (all)               | 39 / 252 (15.48%)<br>39 |  |  |
| Renal and urinary disorders<br>Various renal & urinary<br>subjects affected / exposed<br>occurrences (all)               | 1 / 252 (0.40%)<br>1    |  |  |
| Musculoskeletal and connective tissue disorders<br>Various MSK<br>subjects affected / exposed<br>occurrences (all)       | 4 / 252 (1.59%)<br>4    |  |  |
| Infections and infestations<br>Various infections<br>subjects affected / exposed<br>occurrences (all)                    | 22 / 252 (8.73%)<br>22  |  |  |
| Metabolism and nutrition disorders<br>Various metabolism & nutrition<br>subjects affected / exposed<br>occurrences (all) | 1 / 252 (0.40%)<br>1    |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 14 March 2014     | Substantial amendment 1 - Protocol version 3.0 dated 06 Mar 2014:<br>1) Removal of active placebo arm, trial design amended to 2x2 factorial design.<br>2) Vaccines will be supplied in single units. The use of a replenishment added.<br>3) Accountability of creams and vaccines has been revised to reflect 'Risk-adapted approaches to the management of clinical trials of investigational medicinal products' set out by the MHRA.<br>4) The labelling of creams has been updated in line with exemption of Regulation 46 of The Medicines for Human Use (Clinical Trials) Regulations 2004 SI 1031, subject to MHRA approval. |
| 23 May 2014       | Substantial amendment 2 - Protocol version 4.0 dated 13 May 2014:<br>1) Modified to reflect the use of a non-matching placebo injection syringe for approximately the first 250 vaccine/placebo injection doses and the change of UCL CTU to UCL CCTU.<br>2) The UCL Clinical Trials Unit has been re-named the UCL Comprehensive Clinical Trials Unit. The change of name has been amended throughout the protocol.<br>3) Removal of reference to 'double blind'.<br>4) Clarification of labelling of topical treatments.  |
| 30 September 2014 | Substantial amendment 4: Addition of a site.  |
| 16 October 2014   | Substantial amendment 3: Updated SmPC for Gardasil.   |
| 10 November 2014  | Substantial amendment 5: Addition of two sites.   |
| 01 December 2014  | Substantial amendment 6: Addition of two sites.   |
| 03 February 2015  | Substantial amendment 8: Addition of a site.  |
| 06 February 2015  | Substantial amendment 7: Updated SmPC for Gardasil.   |
| 25 February 2015  | Substantial amendment 9: Poster for use in sexual health clinics.   |
| 03 March 2015     | Substantial amendment 10: Addition of two new sites; removal of one site.   |
| 13 April 2015     | Substantial amendment 11: Updated SmPC for imiquimod.   |
| 21 May 2015       | Substantial amendment 13: Addition of two new sites.  |
| 09 June 2015      | Substantial amendment 12: Updated sIMPD to include glass syringes.  |
| 16 June 2015      | Substantial amendment 14: Addition of a new site.   |
| 04 August 2015    | Substantial amendment 16: Addition of a new site.   |
| 10 August 2015    | Substantial amendment 17: Addition of a new site.   |

|                  |   |
|------------------|---|
| 14 August 2015   | Substantial amendment 15: Updated SmPC for Gardasil.  |
| 29 October 2015  | Substantial amendment 19:<br>1) Use of poster (advertisement materials for research participants) in general practices.<br>2) Addition of Welsh sites and Welsh language provision.<br>3) Addition of three new sites.  |
| 17 November 2015 | Substantial amendment 18: Updated SmPC for Warticon.  |
| 24 December 2015 | Substantial amendment 20: Addition of three new sites.  |
| 02 March 2016    | Substantial amendment 21 - Protocol version 5.0 dated 21 Dec 2015:<br>1. Inclusion of HIV-positive patients who are either on effective anti-retroviral therapy (ART) or have deferred ART, with a CD4 count of more than 500<br>2. The provision of more details of blood sampling (timing, volume of blood) for the peripheral blood mononuclear cells sub-study. Changes to protocol and patient information sheet.<br>3. Specification in the protocol of the timeframe of scheduled visits.<br>4. Clarification in the protocol of when cryotherapy can be used.<br>5. Consent form changes to request permission from HIV-positive patients to use HIV blood test results, and reformatting of the sections requiring only one answer (yes or no).<br>6. Inclusion of a text box on the poster for local site details. The poster without the text box will be made into flyers for distribution within recruiting clinics. |
| 21 March 2016    | Substantial amendment 22: Addition of three new sites.  |
| 26 April 2016    | Substantial amendment 23: Addition of two new sites; change of PI at one site.  |
| 24 June 2016     | Substantial amendment 24: Updated SmPC for Gardasil.  |
| 26 June 2017     | Substantial amendment 25 - Protocol version 6.0 dated 04 May 2017:<br>1) the reduction of the sample size from 1000 to 500 participants and the addition of revised sample size calculations for the two components of the composite primary outcome as important secondary outcomes for each factor.<br>2) Clarification of the secondary outcomes.<br>3) Removal of reference to Stage 2 placebo syringe blinding, which will no longer be performed due to manufacturing issues.   |
| 05 July 2017     | Substantial amendment 26: Letter for participants who miss scheduled trial visits to request follow-up information.   |
| 06 December 2017 | Substantial amendment 27:<br>1) Pregnancy monitoring follow-up consent form and information sheet.<br>2) Six sites to be removed.<br>3) Change of principal investigator at two sites.  |

Notes:

## 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.

Some baseline characteristics (sexual practices, current contraception, previous STIs, wart treatment for last episode, and position of warts were not included in the summary of results as the categories were not mutually exclusive.

Notes:

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30400777>