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 (IMIQ): frequency of dosing reduced to twice a week; frequency of dosing reduced to once a week; if IMIQ was not tolerated at any dose, then IMIQ 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:

Subjects enrolled per age group	
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
Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Number of subjects in period 1	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

Number of subjects in period 1	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:	
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:	
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:	
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:	
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 Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	31	31	32
standard deviation	± 10	± 10	± 10
Gender categorical Units: Subjects			
Female	42	42	43
Male	83	84	83
Previous occurrence of warts Units: Subjects			
None	63	63	63
1 or more	62	63	63
HIV positive Units: Subjects			
Yes	2	4	3
No	123	122	123
Total number of warts 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 Units: Subjects			
Heterosexual	104	102	102
Homosexual	15	20	16
Bisexual	5	4	8
Other	1	0	0
Previous episode(s) of warts Units: Subjects			
Yes	65	68	63
No	60	58	63
Previous treatment for warts (in those with a previous episode) Units: Subjects			
Yes	64	67	63
No	1	1	0
Not applicable	60	58	63
Previous bivalent HPV vaccine Units: Subjects			
Yes	10	12	8
No	115	114	118
Not recorded	0	0	0
Smoking 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 Units: Subjects			
Yes	110	116	119
No	15	10	7
Attended at least one follow-up visit Units: Subjects			
Yes	118	117	109
No	7	9	17
Switched topical treatment at any time Units: Subjects			
Yes	15	15	19
No	110	111	107
Timing of first topical treatment switch 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			
Units: mm			
median	3	3	3
inter-quartile range (Q1-Q3)	2 to 5	2 to 5	2 to 5
Partners in the last 3 months			
Units: Number of partners			
median	1	1	1
inter-quartile range (Q1-Q3)	1 to 1	1 to 2	1 to 1
Number of qHPV doses administered			
Units: Dose			
median	3	3	3
inter-quartile range (Q1-Q3)	3 to 3	2 to 3	3 to 3
Number of STI episodes			
Units: episode			
median	0	0	0
inter-quartile range (Q1-Q3)	0 to 1	0 to 1	0 to 1
Quality of Life - EQ-5D-5L: Health Utility			
Units: health utility			
arithmetic mean	0.94	0.92	0.94
standard deviation	± 0.11	± 0.13	± 0.10
Quality of Life - EQ-5D-5L: Visual analogue scale (VAS)			
Units: score out of 100			
arithmetic mean	83	82	82
standard deviation	± 12	± 13	± 14

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

Total number of warts 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 Units: Subjects			
Heterosexual	102	410	
Homosexual	16	67	
Bisexual	8	25	
Other	0	1	
Previous episode(s) of warts Units: Subjects			
Yes	64	260	
No	62	243	
Previous treatment for warts (in those with a previous episode) Units: Subjects			
Yes	62	256	
No	2	4	
Not applicable	62	243	
Previous bivalent HPV vaccine Units: Subjects			
Yes	13	43	
No	110	457	
Not recorded	3	3	
Smoking 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 Units: Subjects			
Yes	110	455	
No	16	48	
Attended at least one follow-up visit Units: Subjects			
Yes	116	460	
No	10	43	
Switched topical treatment at any time Units: Subjects			
Yes	26	75	
No	100	428	
Timing of first topical treatment switch 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 Units: Subjects			
Yes	16	168	
No	110	335	
Extended PDX beyond 4 weeks (PDX arms only) Units: Subjects			
Yes	80	167	
No	46	85	
Not applicable	0	251	
Any cryotherapy received Units: Subjects			
Yes	68	247	
No	58	256	
Timing of first cryotherapy 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 Units: Subjects			
Yes	9	22	
No	117	481	
Received any treatment from a source outside their treatment centre Units: Subjects			
Yes	6	21	
No	120	482	
Number of vaccines given 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 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 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:

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:

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:

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:

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:

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:

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:

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:

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:

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:

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: participants				
Achieved	35	38	25	30
Not achieved	66	61	73	69

End point values	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

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	IMIQ v PDX
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority[1]
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

Statistical analysis title	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[2]
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

Statistical analysis title	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[3]
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[4]
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

Statistical analysis title	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

Statistical analysis title	Primary analysis
Comparison groups	IMIQ v PDX
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority[5]
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

Statistical analysis title	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

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 acheived	46	35	47	45

End point values	qHPV	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	209	205		
Units: Subjects				
Achieved	128	113		
Not acheived	81	92		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	qHPV v Placebo
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority[6]
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

Statistical analysis title	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

Serious adverse events	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 %

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

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

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

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

subjects affected / exposed occurrences (all)	13 / 252 (5.16%) 13		
Skin and subcutaneous tissue disorders Various skin subjects affected / exposed occurrences (all)	 39 / 252 (15.48%) 39		
Renal and urinary disorders Various renal & urinary subjects affected / exposed occurrences (all)	 1 / 252 (0.40%) 1		
Musculoskeletal and connective tissue disorders Various MSK subjects affected / exposed occurrences (all)	 4 / 252 (1.59%) 4		
Infections and infestations Various infections subjects affected / exposed occurrences (all)	 22 / 252 (8.73%) 22		
Metabolism and nutrition disorders Various metabolism & nutrition subjects affected / exposed occurrences (all)	 1 / 252 (0.40%) 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: 1) Removal of active placebo arm, trial design amended to 2x2 factorial design. 2) Vaccines will be supplied in single units. The use of a replenishment added. 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. 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: 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. 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. 3) Removal of reference to 'double blind'. 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: 1) Use of poster (advertisement materials for research participants) in general practices. 2) Addition of Welsh sites and Welsh language provision. 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: 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 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. 3. Specification in the protocol of the timeframe of scheduled visits. 4. Clarification in the protocol of when cryotherapy can be used. 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). 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: 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. 2) Clarification of the secondary outcomes. 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: 1) Pregnancy monitoring follow-up consent form and information sheet. 2) Six sites to be removed. 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:

Online references

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