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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	VACCAIN-P

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Regular follow-up at outpatient clinic.

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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)	120
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Ineligible (n=80):
- Not meeting inclusion/meeting exclusion criteria (n=77)
- Retracted informed consent (n=1)
- Procedural planning not feasible for patient (n=2)

One patient incorrectly enrolled and excluded

Pre-assignment period milestones

Number of subjects started	126
Number of subjects completed	126

Period 1

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

Blinding implementation details:

Vaccine or placebo prepared by pharmacy.

Arms

Are arms mutually exclusive?	Yes
Arm title	qHPV

Arm description:

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

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

Dosage and administration details:

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

Arm title	placebo
Arm description: placebo injection	
Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

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

Baseline characteristics

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

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

End points

End points reporting groups

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

Primary: Recurrences of HGAIN

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

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

Statistical analyses

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

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

Secondary: Occurrence of LGAIN

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

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

Statistical analyses

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

Secondary: occurrence of anogenital condylomata

End point title	occurrence of anogenital condylomata
End point description: cumulative occurrence of anogenital condylomata at 12 months after last vaccination (FU18)	

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

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

Statistical analyses

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

Adverse events

Adverse events information	
Timeframe for reporting adverse events: first vaccination until 12 months after last vaccination	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	qHPV ITT
Reporting group description: -	
Reporting group title	placebo ITT
Reporting group description: -	

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

none

Notes:

Online references

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