Clinical trial results:
A randomised phase II multi-centre trial of topical treatment in women with vulval intraepithelial neoplasia

Summary

EudraCT number	2006-004327-11
Trial protocol	GB
Global end of trial date	28 April 2014

Results information

Result version number	v1 (current)
This version publication date	09 November 2018
First version publication date	09 November 2018
Summary attachment (see zip file)	2006-004327-11 Synopsis (2006-004327-11_RT3VIN_Annex 1 Synopsis_23 Jan 2018.pdf) 2006-004327-11 Publication (2006-004327-11_RT3VIN Publication_Lancet Oncology 2014.pdf)

Trial information

Trial identification

Sponsor protocol code	SPON 245-06

Additional study identifiers

ISRCTN number	ISRCTN34420460
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	30-36 Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Margherita Carucci, Centre for Trials Research, +44 02920687900, RT3VIN@cardiff.ac.uk
Scientific contact	Chris Hurt, Centre for Trials Research, +44 02920687471, HurtCN@cardiff.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	14 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2013
Global end of trial reached?	Yes
Global end of trial date	28 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether there is evidence that either (or both) of the topical treatments are active, safe and feasible to use, and would therefore warrant further investigation in a phase III setting.

Protection of trial subjects:

The IDMC reviewed the interim data approximately 6 months after the date of randomisation of the first participant. These analyses was carried out to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

SAE reporting was done in real time according to regulatory requirements.

Background therapy:

N/A

Evidence for comparator:

Cidofovir is a nucleoside analogue with antiviral properties and proven activity in comparable disease (cervical intraepithelial neoplasia). In a pilot study of 15 women with cervical intraepithelial neoplasia type 3, seven (47%) of 15 women had a complete response after topical application of the drug. In a pilot study of cidofovir for vulval intraepithelial neoplasia grade 3, four (40%) of ten women had a complete response at the end of follow-up.

Imiquimod is a drug that modifies the immune response. In previous small studies of topical imiquimod (n≤15), a complete response was reported in 28 (41%) of 67 women with vulval intraepithelial neoplasia, but with substantial variation among studies (0–73%).

Actual start date of recruitment	07 October 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 180
Worldwide total number of subjects	180
EEA total number of subjects	180

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)	180
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

180 female participants were recruited from 32 UK sites between 21 Oct 2009 and 11 Jan 2013.

Pre-assignment

Screening details:

Potential participants were given a copy of the PIS and signed a copy of the Consent Form before the screening assessments were carried out to confirm their eligibility. The screening assessments included: Medical history, Assessment of toxicities, Clinical assessment of lesions, Urinalysis, and Pregnancy test (in women with childbearing potential)

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Imiquimod

Arm description:

Imiquimod (5% concentration) was supplied in boxes of 12 individual sachets (one sachet per application). Imiquimod was applied three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread over the whole affected area at night and the area was washed using aqueous cream and water the following day.
Imiquimod was taken from commercial stock. However, as it was used outside of its licensed indication, separate labels were added to the boxes of imiquimod before being dispensed to the sites.

Arm type	Active comparator
Investigational medicinal product name	Imiquimod
Investigational medicinal product code	
Other name	Aldara 5% cream
Pharmaceutical forms	Cream
Routes of administration	Local use

Dosage and administration details:

Imiquimod (5% concentration) was supplied in boxes of 12 individual sachets (one sachet per application). Imiquimod was applied three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread over the whole affected area at night and the area was washed using aqueous cream and water the following day.

Arm title	Cidofovir

Arm description:

Cidofovir was supplied in a 10g tube (1% concentration) containing a six week supply. It was manufactured in a topical formulation by St Marys Pharmaceutical Unit (SMPU), who dispensed the tubes of gel to the local pharmacies. Participants applied Cidofovir three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread to cover the affected area at night and the area was washed using aqueous cream and water the following day.

Arm type	Active comparator
Investigational medicinal product name	Cidofovir
Investigational medicinal product code	
Other name	Vistide
Pharmaceutical forms	Gel
Routes of administration	Local use

Dosage and administration details:

Participants applied Cidofovir three times a week for a period of 24 weeks, unless a complete response

was observed earlier. A thin layer was spread to cover the affected area at night and the area was washed using aqueous cream and water the following day.

Number of subjects in period 1	Imiquimod	Cidofovir
Started	91	89
Completed	69	72
Not completed	22	17
Consent withdrawn by subject	15	10
Physician decision	-	2
Lost to follow-up	5	3
Invalid specimen or biopsy not done	-	2
Invalid speciment or biopsy not done	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Imiquimod

Reporting group description:

Imiquimod (5% concentration) was supplied in boxes of 12 individual sachets (one sachet per application). Imiquimod was applied three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread over the whole affected area at night and the area was washed using aqueous cream and water the following day.
Imiquimod was taken from commercial stock. However, as it was used outside of its licensed indication, separate labels were added to the boxes of imiquimod before being dispensed to the sites.

Reporting group title	Cidofovir

Reporting group description:

Cidofovir was supplied in a 10g tube (1% concentration) containing a six week supply. It was manufactured in a topical formulation by St Marys Pharmaceutical Unit (SMPU), who dispensed the tubes of gel to the local pharmacies. Participants applied Cidofovir three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread to cover the affected area at night and the area was washed using aqueous cream and water the following day.

Reporting group values	Imiquimod	Cidofovir	Total
Number of subjects	91	89	180
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)	91	89	180
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	46	48	
inter-quartile range (Q1-Q3)	41 to 55	42 to 52	-
Gender categorical			
Only female participants were recruited in both arms.			
Units: Subjects			
Female	91	89	180
Imiquimod	0	0	0
Cidofovir	0	0	0

End points

End points reporting groups

Reporting group title	Imiquimod

Reporting group description:

Imiquimod (5% concentration) was supplied in boxes of 12 individual sachets (one sachet per application). Imiquimod was applied three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread over the whole affected area at night and the area was washed using aqueous cream and water the following day.
Imiquimod was taken from commercial stock. However, as it was used outside of its licensed indication, separate labels were added to the boxes of imiquimod before being dispensed to the sites.

Reporting group title	Cidofovir

Reporting group description:

Cidofovir was supplied in a 10g tube (1% concentration) containing a six week supply. It was manufactured in a topical formulation by St Marys Pharmaceutical Unit (SMPU), who dispensed the tubes of gel to the local pharmacies. Participants applied Cidofovir three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread to cover the affected area at night and the area was washed using aqueous cream and water the following day.

Primary: Histologically proven complete response

End point title	Histologically proven complete response[1]

End point description:

End point type	Primary

End point timeframe:

6 weeks after stopping treatment (maximum 30 weeks after starting treatment)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical test was used in the analysis of the primary endpoint of this trial. Each arm used a Flemings single stage design (p0=0.3, p1=0.45, alpha=0.05, power=90%) .

End point values	Imiquimod	Cidofovir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	89		
Units: Patients				
Yes	42	41		
No	49	48		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 6 weeks after end of treatment (maximum 30 weeks)

Adverse event reporting additional description:

Adverse events are assessed by clinical examination every 6 weeks during treatment and 6 weeks after the end of treatment

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Imiquimod

Reporting group description:

Imiquimod (5% concentration) was supplied in boxes of 12 individual sachets (one sachet per application). Imiquimod was applied three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread over the whole affected area at night and the area was washed using aqueous cream and water the following day.
Imiquimod was taken from commercial stock. However, as it was used outside of its licensed indication, separate labels were added to the boxes of imiquimod before being dispensed to the sites.

Reporting group title	Cidofovir

Reporting group description:

Cidofovir was supplied in a 10g tube (1% concentration) containing a six week supply. It was manufactured in a topical formulation by St Marys Pharmaceutical Unit (SMPU), who dispensed the tubes of gel to the local pharmacies. Participants applied Cidofovir three times a week for a period of 24 weeks, unless a complete response was observed earlier. A thin layer was spread to cover the affected area at night and the area was washed using aqueous cream and water the following day.

Serious adverse events	Imiquimod	Cidofovir	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 84 (46.43%)	31 / 84 (36.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	22 / 84 (26.19%)	13 / 84 (15.48%)	
occurrences causally related to treatment / all	2 / 22	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in vulva			
subjects affected / exposed	13 / 84 (15.48%)	16 / 84 (19.05%)	
occurrences causally related to treatment / all	2 / 13	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	10 / 84 (11.90%)	3 / 84 (3.57%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	10 / 84 (11.90%)	11 / 84 (13.10%)	
occurrences causally related to treatment / all	0 / 10	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulceration			
subjects affected / exposed	5 / 84 (5.95%)	4 / 84 (4.76%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Imiquimod	Cidofovir	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 84 (73.81%)	59 / 84 (70.24%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	42 / 84 (50.00%)	38 / 84 (45.24%)	
occurrences (all)	42	38	
Pain in vulva			
subjects affected / exposed	57 / 84 (67.86%)	49 / 84 (58.33%)	
occurrences (all)	57	49	
Headache			
subjects affected / exposed	45 / 84 (53.57%)	34 / 84 (40.48%)	
occurrences (all)	45	34	
Muscle pain			
subjects affected / exposed	45 / 84 (53.57%)	25 / 84 (29.76%)	
occurrences (all)	45	25	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	62 / 84 (73.81%)	59 / 84 (70.24%)	
occurrences (all)	62	59	

Ulceration subjects affected / exposed occurrences (all)	31 / 84 (36.90%) 31	37 / 84 (44.05%) 37	
Metabolism and nutrition disorders Proteinuria subjects affected / exposed occurrences (all)	31 / 84 (36.90%) 31	19 / 84 (22.62%) 19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2008	Protocol Update Version 1.1 dated 30th September to Version 2.0 dated 23rd October 2008. Addition of new PI's/Research sites as follows: • Mike Cohn-Hereford County Hospital • Peter Baldwin-Addenbrookes Hospital • Margaret Cruickshank-Aberdeen Royal Infirmary • Allan MaClean –Royal Free Hospital • Henry Kitchner-St. Marys Manchester • John Tidy-Royal Hallamshire Hospital • Paul Flyn-Singleton Hospital • Pierre-Martin-Hirsch-Royal Preston Hospital • Dirk Brinkmann-St. Marys Portsmouth • Nick Johnson-Royal United Hospital • Omer Devaja-Maidstone Hospital
20 March 2009	Modification of Patient Information Sheets 2 and 3 PIS 2 Version 1.0 (05/02/09) changed to Version 1.2(05/02/09) PIS 3 Version 1.0 (?)changed to Version 1.2(05/02/09) Addition of new PI's/Research sites as follows: • Simon Leeson-Ysbyty Gwynedd • Charles Redman-Uni Hospital of North Staffordshire • Nick Johnson-Royal United Hospital Bath • Elizabeth Derrick- Royal Sussex County Hospital • Ghee-Kheng Chew-Northampton General Hospital • Jill Adams-Torbay Hospital • David Rowen-Royal South Hants Hospital • Margaret Cruikshank-Aberdeen Royal Infirmary • Nagindra Das-Royal Cornwall Hospital • Rahul Nath-Guy's Hospital • Partha Sengupta-Uni Hospital of North Durham • Nailah Nisar-Royal Surrey County Hospital • Janet McLelland-Royal Victoria Infirmary • Simon Leeson-Glan Glwd Hospital
29 May 2009	Addition of new PI's/Research sites as follows: Shelia Pearson-Cumberland Royal Infirmary Frank Lawton-Kings College Hospital Change of PI: Cathy Green-Ninewells Hospital
25 March 2010	Protocol Update Version 2.0 (23/10/08) changed to Version 2.1(Feb 2010). Addition of new PI's/Research sites as follows: • Farhana Ravat-Hillingdon Hospital • Michael Rymer-Worthing Hospital • Marcia Hall-Wexham Park Hospital Change of PI: Steven Attard Montalto-Musgrove Park Hospital

09 November 2010	Protocol Update Version 2.1(Feb 2010) changed to Version 3.0(01-10-2010) • Change of CI from Prof Alison Fiander to Dr Amanda Tristram • Change of Trial Manager from Dr Jeanette Issac to Dr Tracie Madden • Addition of Safety Officer contact details (Mrs Liz Merrifield) PIS 2 Version 1.2 05-02-2009 changed to Version 2.0 01-10-2010 PIS 3 Version 1.2 05-02-2009 changed to Version 2.0 01-10-2010
28 September 2011	Protocol Update Version 3.0 (01 Oct 2010) changed to version 4.0 (01 May 2011): • To clarify the procedures for proteinuria testing • To alter inclusion criteria 3 on lesion size • To clarify the wording around contraception in inclusion criteria 4 • To clarify the instructions on how to take the post-treatment assessment visit biopsy • To clarify rules pertaining to the crossover of patients from one trial arm to the other • To clarify how new lesions should be treated and measured • To update Appendix 1: Response Evaluation Criteria in Solid Tumours • To update the expected adverse reactions with new information from the updated SPCs for imiquimod and cidofovir • To simplify wording used to describe primary outcome measure To alter the name of the Chief Investigator on the imiquimod IMP label To seek approval for the use of Pregnancy Information Sheet and Consent Form Version 1.0 dated 24 Jun 2011 • To state the alternative topical analgesics that can be used in order of preference should there be another national shortage of 5% Lignocaine To add 5 new research sites/Principal Investigators (PIs): • Jonathan Frappell Derriford Hospital • Brett Winter-Roach Salford FoundationTrust Hospital • Usha Natarajan East Surrey Hospital • Bruce Ramsay Peterborough City Hospital • David Pickrell Worcester Royal Hospital To change the PI at 3 existing research sites: • Stephen Attard Montalto-Maidstone Hospital • Kathryn Hillaby-Cheltenham General Hospital • Kathryn Hillaby -Gloucester Royal Hospital • To close Countess of Chester Hospital: • Jeremy Hawe-Countess of Chester Hospital
25 January 2012	To add 3 new research sites/Principal Investigators (PIs): • Clive Gie- Kings Mill Hospital • Tarang Majmudar-Hinchingbrooke Hospital • Alaa Elghobashy-New Cross Hospital To close 2 research sites: • Marcia Hall-Wexham Park Hospital • Charles Redman-University Hospital North Staffordshire To change PI at 2 existing sites: • Alastair Duncan-Northampton General Hospital • Nicholas James Wood-Royal Preston Hospital
15 August 2012	To add 2new research sites/Principal Investigators (PIs): • Karen Gibbon- Whipps Cross University Hospital • Kyle Gilmour –Tameside NHS Foundation Trust

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.

Neither limitations nor caveats were applicable to this summary of the results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25304851

http://www.ncbi.nlm.nih.gov/pubmed/29336101

http://www.ncbi.nlm.nih.gov/pubmed/28600473