Clinical trial results:
Phase II clinical trial investigating the use of epigallocatechin-3-gallate (Veregen) in the treatment of vulval intraepithelial neoplasia

Summary

EudraCT number	2013-003107-19
Trial protocol	GB
Global end of trial date	08 January 2019

Results information

Result version number	v1 (current)
This version publication date	22 January 2020
First version publication date	22 January 2020

Trial information

Trial identification

Sponsor protocol code	13-0288

Additional study identifiers

ISRCTN number	ISRCTN98495886
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CRCTU CAS number: VU2001

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Vincent Drive, Birmingham, United Kingdom, B15 2TT
Public contact	Baljit Kaur, Cancer Research UK Clinical Trials Unit, +44 01214143793, b.kaur@bham.ac.uk
Scientific contact	Baljit Kaur, Cancer Research UK Clinical Trials Unit, +44 01214143793, b.kaur@bham.ac.uk
Sponsor organisation name	Sandwell and West Birmingham Hospitals NHS Trust
Sponsor organisation address	Dudley Road, Birmingham, United Kingdom, B18 7QH
Public contact	Jocelyn Bell, Sandwell and West Birmingham Hospitals NHS Trust, +44 01215074811, jocelyn.bell@nhs.net
Scientific contact	Jocelyn Bell, Sandwell and West Birmingham Hospitals NHS Trust, +44 01215074811, jocelyn.bell@nhs.net

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	16 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2019
Global end of trial reached?	Yes
Global end of trial date	08 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this clinical trial is to determine whether topical application of EGCG (Veregen) can lead to histological resolution of usual type vulval intraepithelial neoplasia (uVIN) when assessed at 32 weeks following the start of treatment. This is done by comparing tissue biopsies taken before and after Veregen treatment.

Protection of trial subjects:

Mild local skin reactions, including erythema, pruritus, irritation (mostly burning), pain and oedema at the site of
application are very common in patients using Veregen to treat genital warts, especially initially, and are likely to be the same in this cohort. Patients will be instructed to use simple analgesia or topical lignocaine an hour before or after treatment. If more severe, there are dose modification directions in the protocol - the number of applications can be reduced to two or one per day or stopped completely. Contraindications listed in the SmPC have been taken into account in the exclusion criteria - participants should not be or become pregnant, breastfeed, take immunosuppressives or be allergic to Veregen or its excipients. Patients who are under clinical suspicion of vulval cancer will have a biopsy for investigative purposes, and can still use the treatment if they wish. Once the diagnosis has been confirmed, they will stop the study treatment immediately for their standard cancer care to begin.

Background therapy:

Research has shown that a compound found in green tea can "switch on" genes which are silenced in cancer. Clinical studies have shown that this compound (EGCG; also known as Veregen) is a safe and effective treatment for vulval warts which are caused by a virus called human papillomavirus (HPV); certain strains of this virus also cause VIN and vulval cancer. This drug has also been shown to prevent the progression of precancerous changes in the mouth, another disease associated with HPV infection. We believe that Veregen could relieve both the symptoms experienced by women with VIN and reduce their risk of progressing to cancer.

Evidence for comparator:

Tumour suppressor genes (TSG) can be silenced during carcinogenesis by DNA promoter methylation and polycomb mediated gene repression. Aberrant TSG methylation has been shown not only in primary VSCC but also in uVIN, suggesting that these changes may occur early during the natural history of the disease. As epigenetic gene silencing is potentially reversible, there is great interest in the development of new therapeutic strategies using epigenetic modulators. Although the prototype inhibitors of DNA methylation, 5-azacytidine, and 5-aza-2’-deoxycytidine have been shown to be efficacious in the treatment of myelodysplastic syndrome (MDS), these agents were found to be ineffective when first used in solid tumours. While it is now thought that this lack of activity was related to the use of too high doses, limited number of days of drug exposure and assessment of response after only one cycle, these drugs also cause significant myelosuppression and are unstable in solution. It could also be argued that epigenetic therapies have failed in solid tumours because they have only been evaluated in patients with advanced disease. Such tumours may have lost epigenetic dependence due to genetic instability. It would follow from this that the use of epigenetic therapies is more likely to be successful in the treatment of early/pre-neoplastic conditions, for example, MDS and possibly uVIN. In vitro studies have

shown that EGCG, can reverse epigenetic silencing and reactivate gene expression in a range of SCC cell lines including one derived from a vulval cancer. Although not as potent a demethylating agent as 5 aza-2'-deoxycytidine, EGCG offers potentially sustained and longer-term exposures with lower toxicity. As uVIN is often characterised by the asynchronous appearance of dysplastic epithelium at multiple sites, the topical application of an effective treatment would offer the benefit of long-term control of a disease otherwise requiring multiple surgical interventions.

Actual start date of recruitment	13 October 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: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	21
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 26 patients were recruited from one UK centre between 13-Oct-2014 and 10-May-2017. The target number of patients to recruit was 56, which was not achieved.

Pre-assignment

Screening details:

Potential patients were identified via the vulval clinic in City Hospital, Birmingham. Patients with a clinical diagnosis of uVIN were informed about the trial and, if histological diagnosis for uVIN was positive, patients would be offered the opportunity to give informed consent. Eligibility would then be determined before enrolling patients.

Period 1

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

Blinding implementation details:

In order to maintain this blind, study medication was labelled with a unique number (Treatment Pack Number) which was then assigned to a patient. Each patient treatment allocation was kept in an Emergency Code Break Envelope inside a locked safe, one based in City Hospital Pharmacy and the other in CRCTU. Unblinding could only be performed for medical reasons. The Chief Investigator or co-investigator were required to give approval before an unblinding was undertaken.

Arms

Are arms mutually exclusive?	Yes
Arm title	Veregen 10% ointment

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Veregen 10% ointment
Investigational medicinal product code	
Other name	EGCG; epigallocatechin-3-gallate
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Patients will be required to apply the ointment three times a day for a maximum duration of 16 weeks. They are advised to apply a small amount of Veregen 10% ointment to each lesion using the fingers, dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the lesions. This should be applied only to affected areas; any application into the vagina, urethra or anus must be avoided.

Arm title	Veregen-matched placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Veregen-matched placebo ointment
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Patients will be required to apply the ointment three times a day for a maximum duration of 16 weeks.

They will be advised to apply a small amount of Veregen-matched placebo to each lesion using the fingers, dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the lesions. This should be applied only to affected areas; any application into the vagina, urethra or anus must be avoided.

Number of subjects in period 1	Veregen 10% ointment	Veregen-matched placebo
Started	13	13
Completed	13	13

Baseline characteristics

Reporting groups	
Reporting group title	Veregen 10% ointment
Reporting group description: -	
Reporting group title	Veregen-matched placebo
Reporting group description: -	

Reporting group values	Veregen 10% ointment	Veregen-matched placebo	Total
Number of subjects	13	13	26
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)	10	11	21
From 65-84 years	3	2	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.62	49.4	
standard deviation	± 12	± 13.2	-
Gender categorical			
Only females were eligible for entry into this trial			
Units: Subjects			
Female	13	13	26
Male	0	0	0
Ethnicity Units: Subjects			
White-British	13	13	26
Smoking Status Units: Subjects			
Current	6	9	15
Never	1	1	2
Previous	6	3	9
First VIN episode? Units: Subjects			
Yes	0	1	1
No	13	12	25
Height Units: cm			
arithmetic mean	161.75	163.11	
standard deviation	± 7.4	± 5.6	-
Weight			

Units: kg			
arithmetic mean	72.03	86.47	
standard deviation	± 11.8	± 31.9	-
Time: first clinical diagnosis to randomisation			
Units: years			
arithmetic mean	8.9	12.66	
standard deviation	± 6	± 10.1	-
Time: first histological diagnosis to randomisation			
Units: years			
arithmetic mean	8.5	12.85	
standard deviation	± 6.7	± 10.5	-
Time: first symptom to randomisation			
Units: years			
arithmetic mean	10.19	14.43	
standard deviation	± 5.9	± 10.2	-
Time: start of current VIN to randomisation			
Units: months			
arithmetic mean	15.33	30.22	
standard deviation	± 16	± 44	-

End points

End points reporting groups

Reporting group title	Veregen 10% ointment
Reporting group description: -	
Reporting group title	Veregen-matched placebo
Reporting group description: -	

Primary: Best histological response

End point title	Best histological response

End point description:

Best histological response observed across the 32 weeks, as established by blinded pathology review, will be used in this assessment. "Responder" defined as a patient who has achieved histological resolution at any point across the 32 weeks and "Non-Responder" defined as a patient who has not achieved histological resolution at any point during the 32 weeks. Histological resolution being defined as the absence of uVIN or invasive disease.

End point type	Primary

End point timeframe:

32 weeks from start date of trial treatment

End point values	Veregen 10% ointment	Veregen-matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: subjects				
Responder	3	3		
Non-responder	6	7		
No response data	4	3		

Statistical analyses

Statistical analysis title	Not Applicable

Statistical analysis description:

The primary end point of best histological response over 32 weeks required descriptive analysis only.

Comparison groups	Veregen 10% ointment v Veregen-matched placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0 [1]
Method	Not applicable
Parameter estimate	Descriptive analysis

Notes:

[1] - p-value is not applicable to this descriptive data set

Secondary: Clinical resolution

End point title	Clinical resolution

End point description:

Best clinical response over the 52 weeks as measured by difference in current lesion size measurement and baseline lesion size. Refer to appendix 1 of EPIVIN protocol for Clinical Response Definitions.

End point type	Secondary

End point timeframe:

Up to 52 weeks from start date of trial treatment

End point values	Veregen 10% ointment	Veregen-matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: subjects				
Complete Response	5	3		
Partial Response	8	2		
Stable Disease	0	6		
Progressive Disease	0	0		
No Response Data	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of cumulative treatment

End point title	Assessment of cumulative treatment

End point description:

Summary statistics will be provided for percentage administered of full treatment, taking into account both dose reductions and interruptions.

End point type	Secondary

End point timeframe:

Up to 16 weeks; end of treatment.

End point values	Veregen 10% ointment	Veregen-matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: Percentage Administered				
arithmetic mean (standard deviation)	69.94 (± 28.50)	86.43 (± 16.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Histological resolution at 16 weeks

End point title	Histological resolution at 16 weeks

End point description:

Best histological response observed up to 16 weeks, as established by blinded pathology review, will be used in this assessment. "Responder" defined as a patient who has achieved histological resolution at any point across the 16 weeks and "Non-Responder" defined as a patient who has not achieved histological resolution at any point during the 16 weeks. Histological resolution being defined as the absence of uVIN or invasive disease.

End point type	Secondary

End point timeframe:

16 weeks from start of treatment

End point values	Veregen 10% ointment	Veregen-matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: Subjects				
Responder	2	3		
Non-responder	7	7		
No response data	4	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Details of all Adverse Events will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

Adverse event reporting additional description:

Adverse events are collected on a case report form at each visit and returned to the Trial Office. Serious Adverse Events are reported immediately (within 24 hours of becoming aware) by the investigator who sends a signed SAE form to the Trial Office. All SAE's must be reported whether it is thought to be related to trial treatment or not.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Veregen arm

Reporting group description:

Patients randomised to receive Veregen 10% treatment

Reporting group title	Placebo arm

Reporting group description:

Patients randomised to receive Veregen-matched placebo treatment

Serious adverse events	Veregen arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (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: 0 %

Non-serious adverse events	Veregen arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	12 / 13 (92.31%)	
General disorders and administration site conditions			

bleeding			
subjects affected / exposed	2 / 13 (15.38%)	3 / 13 (23.08%)	
occurrences (all)	2	5	
Localised Swelling			
subjects affected / exposed	2 / 13 (15.38%)	0 / 13 (0.00%)	
occurrences (all)	6	0	
Localised oedema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Malaise			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	11 / 13 (84.62%)	7 / 13 (53.85%)	
occurrences (all)	22	19	
General disorders and administration site conditions - Other, specify			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
cough			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Laryngeal Hemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Erythema multiforme			
subjects affected / exposed	8 / 13 (61.54%)	2 / 13 (15.38%)	
occurrences (all)	9	7	
Burning sensation			
subjects affected / exposed	8 / 13 (61.54%)	4 / 13 (30.77%)	
occurrences (all)	11	5	
exfoliation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	4	0	
Pruritus			
subjects affected / exposed	10 / 13 (76.92%)	9 / 13 (69.23%)	
occurrences (all)	26	27	
Rash acneiform			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
skin ulceration			
subjects affected / exposed	2 / 13 (15.38%)	1 / 13 (7.69%)	
occurrences (all)	4	2	
sore around area			
subjects affected / exposed	11 / 13 (84.62%)	4 / 13 (30.77%)	
occurrences (all)	18	5	
tingling			
subjects affected / exposed	0 / 13 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	2 / 13 (15.38%)	4 / 13 (30.77%)	
occurrences (all)	3	4	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2015	• Clarification of the fraction of biopsy that will be reviewed • Removal of RECIST method to assess clinical response • Appendix 1 amended to reflect change in Clinical Evaluation • Removal of colour photography requirement • Addition of stratification variable • Clarification of the definition of histological resolution • Clarification of timing of screening biopsy • Removal of Record of Birth Control at week 32 follow up assessment • Added review of concomitant medication in for weeks 4, 8 and 16 • Clarification of the definitions of Patient Withdrawal • Clarification of secondary endpoints • Added description of placebo • Highlighted that sample collection is mandatory • Described use of the HBRC for baseline biopsy
14 September 2015	• Amendment to eligibility criteria, clarification of terms used in histological diagnosis of uVIN or VIN3 and exclusion of patients with severe liver dysfunction or chronic liver disease • Updated concomitant medication advice • Removed need to permanently stop trial treatment if more than 6 continuous days missed Other non-substantial modifications: • Updated Data Monitoring Committee scheduled meeting dates • Removal of Professor Ciaran Woodman's name from signature page and clarification of his role in the trial • Correction of typographical errors
05 February 2016	Recruitment halt in order to relabel IMP. Protocol updated accordingly.
15 July 2016	• Clarification of primary and secondary outcome measures • Modification of "intention to treat" rule • Modification of evaluation of response criteria • Updated Trial Management Group personnel details • Proportion of biopsies for independent review increased
30 November 2016	Clarification of evaluation of response criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

12 January 2016	Placebo IMP was due to expire however stability data was produced by Medigene AG to support extension of placebo IMP from February 2016 to January 2018. IMP was relabelled accordingly and recruitment was then able to resume.	07 April 2016
12 May 2016	Active IMP was due to expire however stability data was produced by Medigene AG to support extension of the Active IMP from August 2016 to June 2019. IMP was relabelled accordingly and recruitment was then able to resume.	23 September 2016

Notes:

Limitations and caveats

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

The trial failed to recruit to its specified target of 56 patients. Analysis of outcomes was therefore underpowered.

Notes: