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► **To cite this version:**

Richard Gilson, Jonathan Ross, Raymond Maw, David Rowen, Christopher Sonnex, et al.. A multi-centre, randomised, double-blind, placebo-controlled study of cryotherapy versus cryotherapy and podophyllotoxin cream as treatment for external anogenital warts.. *Sexually Transmitted Infections*, 2009, 85 (7), pp.514. 10.1136/sti.2009.038075 . hal-00552823

HAL Id: hal-00552823

<https://hal.science/hal-00552823>

Submitted on 6 Jan 2011

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A multi-centre, randomised, double-blind, placebo-controlled study of cryotherapy versus cryotherapy and podophyllotoxin cream as treatment for external anogenital warts.

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Keywords: genital warts, podophyllotoxin, cryotherapy, treatment.

ABSTRACT

Objectives: To compare the efficacy and safety of combination therapy with cryotherapy and podophyllotoxin 0.15% cream versus cryotherapy alone in the treatment of anogenital warts.

Methods: A randomised, double-blind, multi-centre controlled trial. Patients received podophyllotoxin cream or placebo twice daily for 3 days/week for up to 4 weeks, with weekly cryotherapy continued to week 12 if required. Further treatment from week 12-24 was discretionary. Patients were stratified by sex and history of warts. HIV-positivity, warts treated in the past 4 months, or warts with a combined area of $<10\text{mm}^2$ were exclusion criteria. Primary endpoints were clearance at week 4 and 12.

Results: 70 patients per group were randomised and started treatment; 101 first-episode warts, 91 male. No treatment-related serious adverse events were reported. Follow-up at week 12 was 85%. By intention-to-treat analysis, clearances at 4 and 12 weeks were higher in the combination group (60.0% and 60.0% respectively) than with cryotherapy alone (45.7%, 45.7%) although not statistically significant (relative risk 1.31; 95% CI 0.95, 1.81). By week 24 there was no difference between the groups (68.6% and 64.3% respectively, RR 1.07; CI 0.84, 1.35). At week 4, wart clearance was higher in men ($p=0.001$) and those with a past history of warts ($p=0.009$), but these differences were not detected at week 12. There was some evidence for a higher relapse rate in the group receiving cryotherapy alone.

Conclusions: Initial combination therapy with podophyllotoxin/cryotherapy was well tolerated and may have resulted in earlier clearance in some patients, compared to cryotherapy alone, however overall differences in clearance rates were not statistically significant.

INTRODUCTION

Anogenital warts, which are caused in most cases by infection with human papillomavirus (HPV) type 6 or 11, are the most frequently diagnosed sexually transmitted infection in sexual health clinics in the UK.¹ Although not associated with serious morbidity, they cause significant detriment to health-related quality of life. Treatment can be uncomfortable for the patient, and often requires several visits to the clinic. It consumes substantial health service resources and ways to limit this, and improve treatment outcomes for patients, need to be explored. All available treatments have limited efficacy and relapse is common.²

In sexual health clinics several ablative therapies are used, including cryotherapy, trichloroacetic acid and local excision. Cryotherapy alone is used most frequently³ and has a reported efficacy of 79-88% for wart clearance, but as with all therapies relapse or recurrence is frequent, occurring in 25-39% of cases.⁴⁻⁶ Multiple attendances are often needed which increases the burden on both patients and clinic resources. Both podophyllotoxin and imiquimod are available for self-application at home, are generally well tolerated, and have similar efficacy to cryotherapy.^{2,7,8}

A combination of cryotherapy and podophyllotoxin is used in clinics, but has never been formally evaluated. One comparative study which included combination treatment with the unpurified preparation podophyllin and cryotherapy,⁹ demonstrated no additional benefit over cryotherapy alone. Podophyllin has to be applied in the clinic, is of variable potency, and is no longer recommended in British¹⁰ or European guidelines.¹¹ Combining cryotherapy with podophyllotoxin may improve the clearance rate, or achieve a more rapid response. This may be worthwhile even though it requires more clinic visits than

home applied therapy alone. However, it may be associated with more adverse effects, principally pain and soreness. If these are still tolerated by the patient this may be acceptable, but if the adverse effects are sufficient to compromise adherence, or otherwise limit treatment, there may be a reduction in overall efficacy.

A double-blind randomised controlled trial was undertaken to compare the efficacy and safety of cryotherapy and podophyllotoxin cream versus cryotherapy alone in the treatment of anogenital warts.

METHODS

A randomised, double-blind, placebo-controlled study comparing cryotherapy and podophyllotoxin with cryotherapy and placebo (cryotherapy alone) was conducted at five sexual health clinics (see list below). Podophyllotoxin was administered as a 0.15% cream (Wartec[®]/Warticon[®], Stiefel) or matching placebo.

All patients received cryotherapy, applied using a liquid nitrogen spray (Cry-Ac, Brymill Cryogenic Systems, UK) to obtain a minimum of a 45 second freeze (from start of application), repeated after a thaw in a standardised manner. Cryotherapy was repeated weekly for up to 12 weeks. Starting the day after the cryotherapy, podophyllotoxin cream or placebo was applied twice daily for 3 consecutive days, and repeated weekly for up to four weeks, or until all warts had cleared if earlier. If further treatment was required, only cryotherapy was used between week 4 and week 12., but after week 12 treatment was at the discretion of the clinician.

Patients were evaluated at baseline when the number, size (area judged against a calibration template), location and type (hyperkeratotic, non-keratotic, mixed; reference images were provided) of warts were documented. Follow-up assessments were performed at clinic visits at weeks 1, 2, 3, 4, 12 and 24, when wart clearance, relapse, and new warts were recorded separately, as well as treatment adherence. If patients did not attend for follow-up assessments, they were contacted by letter and telephone and encouraged to re-attend. If this failed, self-assessed clearance was recorded, together with information on any treatment received outside of the trial. Self-assessment was documented on a proforma returned by the patient to the clinic, or by the investigator after a telephone interview.

Principal entry and exclusion criteria: Entry requirements were age 18-70 years, male and female patients with at least two (maximum 30) external anogenital warts with a combined area of at least 10mm², which in the opinion of the investigator could be appropriately treated with cryotherapy with or without podophyllotoxin cream. Warts were either previously untreated, or not treated for at least four months.

Patients were excluded if known to be HIV-positive (HIV testing was not a requirement), had concurrent internal anogenital warts, or had individual warts >4cm² in area.

Sample size calculation: The sample size for the study was based on an estimate of a 45% response rate in the cryotherapy alone arm and a 70% response in the podophyllotoxin combination arm. Sixty eight patients in each group would have provided 80% power to detect such a difference, or 85 patients after allowing for a 20% loss to follow-up (170 patients in total).

Randomisation and analysis: Patients were randomised in equal numbers to each group, stratified by sex and history of anogenital warts, in blocks of four. Treatment packs were supplied pre-labelled by the clinical trials unit at the manufacturer (Stiefel). Study numbers and corresponding treatment packs were then allocated in sequence by site investigators, against a local register. Blocks were reallocated between centres if required by the rate of recruitment. The primary endpoints were clearance of all anogenital warts at four and 12 weeks, including warts that had been present at baseline and any warts that may have appeared, or recurred, during follow-up. Secondary endpoints were clearance at 24 weeks, recurrence at 12 weeks in those cleared at 4 weeks, and recurrence at 24 weeks in those clear at 12 weeks.

The statistical analysis plan was defined prior to data processing. Primary and secondary endpoint analyses were to be performed on an intention-to-treat population comprising those patients who were randomised, received at least one cryotherapy treatment and attended at least one follow-up assessment. In the event of an observation being missing (due to non-attendance) the analysis would use the last observation carried forward (LOCF) process to impute the status at subsequent time points. This assumes that patients who had cleared warts had not relapsed or developed new warts, and those that had not cleared did not do so over the period in question. To see the effect of using LOCF, clearance rates are also reported using only observed data at each time point.

The primary efficacy endpoints are summarised by treatment group and visit, with differences between the groups investigated by linear logistic regression analysis, adjusted for randomization group, centre and treatment group. An exploratory analysis of the primary outcome measure was planned, using a linear logistic regression model

adjusting for randomization group, centre, baseline wart area and history of warts, and any covariates significant at a 10% level in the univariate analysis. Further sub-group analyses were permitted but, given the small numbers, these would be exploratory and interaction effects would not be investigated.

Consent and approval: All patients gave written informed consent and the study was reviewed by the London Multicentre Research Ethics Committee. The study was monitored by an independent data and safety monitoring committee (DSMC), including a planned review of interim results with respect to efficacy and statistical power.

RESULTS

Study recruitment was stopped at 149 patients, of whom 140 (70 in each group) started treatment and attended for at least one follow-up visit (intention-to-treat population). In the patients randomised to podophyllotoxin combination or cryotherapy alone, respectively, 67.1% and 62.9% were male, and 30.0% and 25.7% had a previous history of anogenital warts (Table 1). Patients in the combination arm had a higher proportion of keratotic warts and the estimated area of warts was larger.

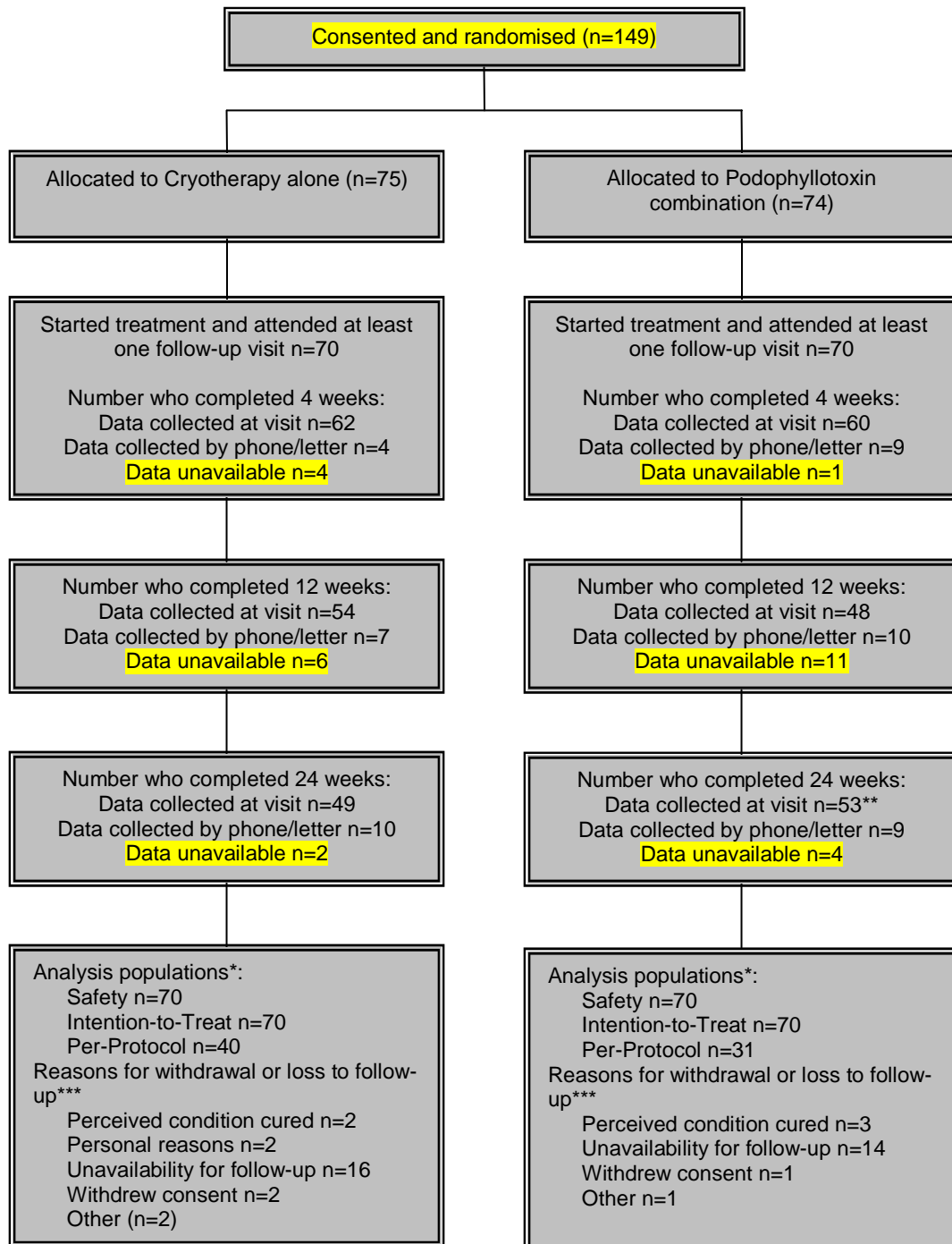
Table 1 Baseline characteristics

	Podophyllotoxin combination	Cryotherapy alone
Number	70	70
Age: Median (range)	26 (18-58)	24.5 (18-43)
Sex: n (%) Male	47 (67.1)	44 (62.9)
Ethnicity: n (%)		
White	61 (87.1)	63 (90.0)
Black	5 (7.1)	6 (8.6)
Other	4 (5.7)	1 (1.4)
Circumcision status in males n (%)		
Circumcised	11 (23.4)	7 (15.9)
Uncircumcised	36 (76.6)	37 (84.1)
Heterosexual n (%)	65 (92.9)	67 (95.7)
Smoker n (%)	37 (52.9)	43 (61.4)
History of warts: n (%)		
First episode	49 (70.0)	52 (74.3)
Previous history	21 (30.0)	18 (25.7)
Location of warts: n (%)		
Anal only	7 (10.0)	4 (5.7)
Non-anal only	52 (74.3)	55 (78.6)
Both anal and non-anal	11 (15.7)	11 (15.7)
Type of warts: n(%)		
Keratotic	25 (35.7)	12 (17.1)
Non-keratotic	29 (41.4)	38 (54.3)
Mixed	16 (22.9)	20 (28.6)
Number of warts		
Median (range)	7 (2-30)	6.5 (2-34)
Estimated total area of warts (mm ²)		
Median (range)	49.5 (10-400)	38.0 (12-464)

Notes: Recruitment period 2005-06. Recruitment at each Treatment Centre 1 to 5: n= 44, 23, 29, 37, 7 respectively.

With the addition of self-reports, information was available on 119 (85.0%) at week 12 and 121 (86.4%) at week 24. Use of study cream declined over the four weeks of the blinded phase of the treatment protocol, to 31.1% in the podophyllotoxin combination and 54.8% in the cryotherapy alone (placebo cream) group; application of cryotherapy or cream was recorded in 42.9% and 61.4% respectively in the 4th week of follow-up. Reasons for withdrawal and the number followed-up are detailed in Figure 1.

Figure 1 Study Flow Diagram



* The safety population included all patients randomized who received at least one cryotherapy treatment and one application of blinded medication. The intention-to-treat population included all patients who were randomized, had at least one treatment, and

had at least one follow-up assessment. The per-protocol population comprised all those in the ITT population who did not have a major protocol violation, principally non-attendance for follow-up. ITT efficacy analyses used last observation carried forward as described in the Methods.

** Numbers with observed data increased where patients missed an earlier assessment but re-attended for later time points

*** patients may have had more than one reason for withdrawal.

Clearance rates at weeks 4 and 12, the primary end-points, were 60.0% at both times in the podophyllotoxin combination group, and 45.7% at both times in the cryotherapy alone group, but these differences were not statistically significant (relative risk 1.31; 95% confidence interval 0.95, 1.81). The clearance rate at week 24 was very similar in both groups (68.6% and 64.3% respectively; RR 1.07; CI 0.84, 1.35). When adjusted for baseline number and area of warts, history and treatment centre differences between the groups remained non-significant (Table 2).

Loss to follow-up was similar in both groups, but comparison of the LOCF and observed data indicates that the clearance rate was lower in those subsequently lost to follow-up, particularly in the cryotherapy alone arm (Table 2).

Table 2: Anogenital wart clearance; intention-to-treat analysis using last observation carried forward and observed data only.

	Podophyllotoxin combination	Cryotherapy alone	Unadjusted OR*	Adjusted OR**
	(n=70)	(n=70)	(95% CI) p value	(95% CI) p value
Week 4 n (%) cleared	42 (60.0)	32 (45.7)	1.78 (0.91, 3.48) p=0.09	1.99 (0.91, 4.36) p=0.085
[observed data]	[40/66; 60.6%]	[31/64; 48.4%]		
Week 12 n (%) cleared	42 (60.0)	32 (45.7)	1.78 (0.91, 3.48) p=0.09	1.94 (0.95, 3.97) p=0.069
[observed data]	[34/56; 60.7%]	[30/59; 50.8%]		
Week 24 n (%) cleared	48 (68.6)	45 (64.3)	1.21 (0.60, 2.45) p=0.59	1.18 (0.56, 2.49) p=0.67
[observed data]	[43/59; 72.9%]	[41/57; 71.9%]		

* Odds ratio for podophyllotoxin combination versus cryotherapy alone.

** Adjusted for baseline number and area of warts, history and treatment centre

In a multivariate analysis of factors associated with wart clearance, there were associations with history of warts and sex (Table 3). At week 4, patients with a prior history of warts were more likely to clear ($p=0.009$) than patients for whom this was their first diagnosed episode, although this effect was not seen at week 12. Consequently, an exploratory analysis of clearance rates was performed, split by wart history. At week 4, patients with a prior history of warts were more likely to have cleared with the podophyllotoxin combination (unadjusted odds ratio 4.80; CI 1.03, 22.3; $p=0.045$), however at week 12, the effect was no longer significant (2.03; CI 0.56, 7.31; $p=0.28$). In

the group with a first episode of warts, there was no difference in clearance at week 4 or week 12 by treatment allocation (OR 1.31; CI 0.60, 2.87; $p=0.50$ at week 4, and OR 1.69, CI 0.77, 3.72; $p=0.19$ at week 12 with podophyllotoxin combination versus cryotherapy alone respectively).

At week 4, males were more likely to show clearance than females ($p=0.001$). However in a further analysis of data split by sex, the unadjusted OR for podophyllotoxin combination therapy versus cryotherapy alone were similar in men and women and not significant (OR 1.75; CI 0.52, 5.82; $p=0.37$ for females and 1.79; CI 0.76, 4.25; $p=0.19$ for males). At week 12, females were more likely to have cleared with podophyllotoxin combination, but this was of borderline statistical significance (OR 3.12; CI 0.96, 10.2; $p=0.059$). There was no effect in males (OR 1.36; CI 0.59, 3.09; $p=0.47$).

Table 3: Factors associated with wart clearance rates at 4 and 12 weeks
(multivariate analysis of ITT population with last observation carried forward)

Comparison	Week 4		Week 12	
	Adjusted OR (95% CI)	p value	Adjusted OR (95% CI)	P value
Treatment Podophyllotoxin combination	1.99 (0.91, 4.36)	P=0.085	1.94 (0.95, 3.97)	p=0.069
Cryotherapy alone	1.00		1.00	
Baseline no. of warts	0.95 (0.88, 1.03)	P=0.25	0.95 (0.88, 1.03)	P=0.22
Baseline area of warts	1.00 (0.99, 1.00)	P=0.16	1.00 (0.99, 1.00)	P=0.56
History of warts First episode	0.29 (0.11, 0.74)	P=0.009	1.13 (0.51, 2.53)	p=0.76
Previous history	1.00		1.00	
Sex Female	0.23 (0.10, 0.56)	P=0.001	1.31 (0.61, 2.84)	p=0.49
Male	1.00		1.00	

The effect of podophyllotoxin combination treatment was also investigated in an exploratory analysis according to wart type. Ablative therapies have been recommended in preference to topical agents for more highly keratinized warts,¹⁰ but combination therapy might be still more effective. When analysed separately, there was no difference between the effect of podophyllotoxin combination therapy in patients classified as

having either hyperkeratotic or non-keratotic warts at week 4 (OR 1.5; CI 0.38, 6.00 and 1.38; CI 0.51, 3.76 respectively), or at week 12 (OR 1.29; CI 0.32, 5.19 and 1.24; CI 0.45, 3.38).

More patients receiving the podophyllotoxin combination had at least a 50% reduction in wart area by weeks 4 and 12, but this difference was not statistically significant (data not shown). There was some evidence for patients in the cryotherapy alone arm experiencing a greater number and larger area of new and/or relapsed warts. Between week 4 and week 12, more patients who had cleared warts at week 4 in the cryotherapy alone arm had new or recurrent warts noted at week 12, compared to the podophyllotoxin combination arm although this was not statistically significant (11/32, 34.4% versus 12/42, 26.6%; $p=0.67$). After week 12, further treatment in both groups was at the discretion of the physician (who remained blinded to the earlier treatment allocation). Recurrence rates between week 12 and week 24 were similar (6/32, 18.8% and 7/42, 16.7%, respectively).

There were no treatment-related serious adverse events. The proportion of patients experiencing any adverse event was similar in both groups (72.9% podophyllotoxin combination, 70.0% cryotherapy alone; $p=0.85$). Application site events occurred more frequently in the combination group (64.3% versus 44.3%; $p=0.027$), with pain being the most frequent event in both groups (34.3% versus 18.6%; $p=0.055$). No patient withdrew from the study because of treatment-related local events, but more patients in the podophyllotoxin combination arm ($n=13$, 18.6%) stopped blinded study medication than in the cryotherapy alone arm ($n=4$, 5.7%; $p=0.036$).

DISCUSSION

Cryotherapy and podophyllotoxin are used in combination in current practice, but this has not been evaluated before in a randomised controlled trial. Overall, there was no statistically significant difference between the treatments with respect to the primary endpoints of clearance of warts at 4 and 12 weeks. There was some evidence for an improved outcome with podophyllotoxin combination treatment, with about a third increase in the chance of clearing warts by 4 and 12 weeks (60.0% versus 45.7%; relative risk 1.31). Clearance at the end of 24 weeks, during which further treatment could be given at the discretion of the clinician, was similar in both groups (68.6% podophyllotoxin combination; 64.3% cryotherapy alone). Clearance was defined as resolution of both warts present at baseline and any new or relapsed warts observed during follow-up. These results are consistent with published reports on podophyllotoxin or cryotherapy alone.^{11;12} The incidence of new or relapsed warts appearing after the end of the blinded treatment phase favoured the podophyllotoxin combination arm but the difference was not statistically significant.

One study has investigated combination therapy with cryotherapy and podophyllin, rather than podophyllotoxin, in an open comparative trial in which treatment allocation for patients starting treatment was changed at random at weekly intervals.⁹ The study included 409 patients; 76 received cryotherapy and podophyllin, and 85 received trichloroacetic acid and podophyllin (the remainder received monotherapy). Either combination therapy (podophyllin 77.6%; trichloroacetic acid 74.1%) was more effective than podophyllin alone (58.2%), but similar to cryotherapy alone (75.3%). This study did not include use of podophyllotoxin, which is more effective than podophyllin.⁷

The population recruited in this study was mixed, with males and females and first episode as well as repeat cases and few entry restrictions, to reflect as nearly as possible routine clinical practice. Randomisation was stratified by sex and history of warts, both factors shown to be related to treatment response. Men appeared to be responding better at 4 weeks, but there was no difference at 12 or 24 weeks. Similarly those with a history of warts responded better. This may reflect a difference in immunological status in those with prior HPV-related disease. Although the groups were well matched on the stratification criteria, there were more patients with keratotic warts in the group given podophyllotoxin combination therapy. Current treatment guidelines recommend the use of ablative therapies for keratinised warts;¹⁰ in this study, there was no evidence of a difference in the treatment response according to the type of wart, although the number available for this sub-group analysis was small.

Podophyllotoxin combination therapy was well tolerated. There were more reports of application site events in the combination treatment group but this is to be expected and consistent with an additive effect of using podophyllotoxin. More patients discontinued use of the cream in the active treatment group (18.6% versus 5.7%).

The study achieved high follow-up rates, including the use of patient reported assessments for those study subjects who missed follow-up evaluations in clinic. We used an analysis based on last observation carried forward to account for missing assessment data. This may overestimate the effect of treatment if clearance is followed by early relapse and this is not captured due to missed assessments. More patients failed to attend for follow-up in the podophyllotoxin combination arm, but this was largely compensated for by additional self-reports. Follow-up rates are critical to the reliability of evaluations of wart treatments.⁷ Self-assessment may underestimate the presence of

persistent or recurrent warts.¹³ Nonetheless the simple end-point of complete clearance may be less likely to lead to misclassification. Future studies based on a similar design but with fewer follow-up assessments may allow even higher follow-up rates, thus allowing wart treatments to be evaluated more easily and reliably in larger populations, providing greater statistical power.

Although patients receiving podophyllotoxin combination therapy had almost one third greater chance of clearance this difference did not reach statistical significance. At a planned interim review by the DSMC it was noted that the response rate in the comparator arm at 4 weeks was lower than predicted in the study design. This led to a recommendation that the number of patients recruited should be increased, but neither time nor resources were available to allow this. A substantially larger study would have been required to confirm whether combination therapy was indeed superior, or to exclude an important treatment effect. There remains the possibility that podophyllotoxin combination therapy may benefit at least some patients; further work is required to refine optimum treatment regimens.

Key messages

- There was some evidence for improved clearance rates when podophyllotoxin was used for up to 4 weeks in combination with cryotherapy but the difference was not statistically significant as compared to cryotherapy alone after 4 or 12 weeks.
- Podophyllotoxin combination therapy was well tolerated.
- After 12 weeks, patients had further treatment at the discretion of the clinician; clearance rates assessed at 24 weeks were very similar in both groups.

Acknowledgements: The authors wish to thank the patients and staff at the clinics involved. The study was initiated by the HPV Special Interest Group of the British Association for Sexual Health and HIV and supported by Stiefel International Research and Development. The help of the Data and Safety Monitoring Committee (Dr A. McMillan, Dr N. Thin, Professor A. Nunn) and Dr S. Barton as chairman of the Trial Steering Committee, is gratefully acknowledged. Professor Nunn advised on the design of the study, the analysis plan and the report, as well as chairing the DSMC.

Funding: This was an investigator-led study funded by Stiefel International R&D.

Author contributions: RJCG and CJNL led the design of the study in consultation with the sponsors; RJCG was principal investigator at one centre, and drafted the manuscript. JR, RM, DR and CS were site investigators, commented on the design of the study and the report.

Study sites: Department of Genitourinary Medicine, Camden Primary Care Trust, The Mortimer Market Centre, London; Camden PCT; Whittall Street Clinic, Birmingham; Royal Victoria Hospital, Belfast; Royal South Hampshire Hospital, Southampton; Addenbrooke's Hospital, Cambridge.

Disclosure: None of the authors are employees of, or consultants to Stiefel Laboratories Inc.

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Word count: 2753

Abstract 230

Number of Figures: 1

Number of Tables: 3

Number of References: 13