Clinical trial results:
A Randomised Controlled Trial of Adjunctive Systemic Therapy for Vulval Erosive Lichen Planus

Summary

EudraCT number	2014-000547-32
Trial protocol	GB
Global end of trial date	10 March 2016

Results information

Result version number	v1 (current)
This version publication date	09 March 2017
First version publication date	09 March 2017

Trial information

Trial identification

Sponsor protocol code	13123

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Lenton Lane, Nottingham, United Kingdom, NG7 2NR
Public contact	CI, Kim Thomas, +44 01158468632, kim.thomas@nottingham.ac.uk
Scientific contact	CI, Kim Thomas, +44 01158468632, kim.thomas@nottingham.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	17 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2016
Global end of trial reached?	Yes
Global end of trial date	10 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess whether the addition of systemic therapies are better than topical treatment (in conjunction with a short course of oral corticosteroids) in treating patients with ELPV that has not responded to standard first-line topical therapy. The trial will be statistically powered to assess whether the additional systemic therapy is more effective than the control treatment, it will not be powered to assess which of the three additional therapies is the most effective.

Protection of trial subjects:

An individual participant will stop treatment (but continue follow up) if:
- they have poor ongoing control of disease despite good adherence to the treatment regimen and optimising topical clobetasol propionate 0.05% use and the clinician feels it is unethical to continue; or
- side effects indicate that the participant should not carry on with the designated treatment regimen.
Please note - Specifically for patients taking mycophenolate mofetil if neutropenia develops (absolute neutrophil count < 1.3 x 10^3) treatment should be discontinued.
If participants stop the study treatment they will continue to be followed up.
Participants may stop the trial early either at their own request or at the Investigator's discretion (for example due to severe secondary infection, pregnancy and development of malignancy). If possible data will continue to be collected. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they stop the trial, data collected to date cannot be erased and will still be used in the final analysis.
Participants who are randomised but are subsequently found to be ineligible will be replaced and will not be included in the intention to treat analysis. Participants who are randomised but choose not to start their medication (i.e. change their mind re: participation) will be followed up and will be included in the intention to treat analysis.

Background therapy:

None. All participants receive clobetasol as per usual care.

Evidence for comparator:

First-line therapy in the UK is with a super-potent topical steroid, usually clobetasol propionate 0.05% [16, 17]. Non-randomised studies, mainly retrospective case series, have suggested that super-potent topical steroids can be an effective first-line therapy [10, 12, 18, 19]. However, in the only prospective published case series [10], one-third of patients responded poorly to super-potent topical steroids. Evidence to date suggests that super-potent topical steroids are a reasonable first-line therapeutic choice and qualitative work has shown that they are ingrained into clinical practice as an initial therapy for ELPV [20]. The rationale for using clobetasol propionate 0.05% in all groups is determined from collaboration with the British Society for the Study of vulThere is no agreement for which second-line agents should be used [7, 17], despite the fact that one-third of patients fail first-line therapy. Most second-line therapies are used based upon expert opinion. Systemic agents described in case series and case reports consist of:
- oral corticosteroids
- systemic immunosuppressants including azathioprine, ciclosporin, methotrexate and mycophenolate mofetil
- systemic antibiotics, particularly tetracyclines
- hydroxychloroquine
- oral retinoids
- other anti-inflammatory agents including griseofulvin (an oral anti-fungal agent), colchicine (an agent traditionally used to treat gout) and dapsone.

vovaginal disease (BSSVD) and limited case series studies in the literature.

Actual start date of recruitment	01 May 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	United Kingdom: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place over 14 months (1st June 2014 to 31st July 2015) at 12 United Kingdom National Health Service hospital outpatient departments. Follow-up was for 12 months.

Pre-assignment

Screening details:

Women aged 18 or over with a clinical diagnosis of moderate to severe ELPV, despite treatment for three-months with clobetasol propionate 0.05%, were included. A vulval biopsy that excluded malignant/pre-malignant disease must have been documented. Participants had to agree to clinical photographs being taken and, if relevant, agree to use effectiv

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	Control group

Arm description:

standard care of topical clobetasol propionate 0.05% plus a short course of oral prednisolone. N.B Topical clobetasol propionate 0.05% will be used once daily for one month, alternate days for 1 month then twice weekly thereon. This is in conjunction with an initial reducing course of oral prednisolone (20mg per day to reduce by 5mg per week over 4 weeks until stop (i.e. 20mg/day for 1 week, then 15mg/day for 1 week, then 10mg/day for 1 week, then 5mg/day for 1 week then stop)

Arm type	Active comparator
Investigational medicinal product name	Clobetasol prorionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Topical clobetasol propionate 0.05% will be used once daily for one month, alternate days for 1 month then twice weekly thereon.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

reducing course of oral prednisolone (20mg per day to reduce by 5mg per week over 4 weeks until stop (i.e. 20mg/day for 1 week, then 15mg/day for 1 week, then 10mg/day for 1 week, then 5mg/day for 1 week then stop)

Arm title	Research arm 1

Arm description:

Oral hydroxychloroquine (up to 200mg twice daily) PLUS topical clobetasol propionate 0.05%% in the same regimen as in the control group. The exact dose will be decided by the treating physician according to clinical requirement. Oral hydroxychloroquine shoRuld be used as per usual practice following national guidelines including appropriate safety monitoring.

Arm type	Experimental

Investigational medicinal product name	Clobetasol prorionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Topical clobetasol propionate 0.05% will be used once daily for one month, alternate days for 1 month then twice weekly thereon.

Arm title	Research arm 2

Arm description:

Oral methotrexate (starting at 5mg weekly titrated upwards over 3-4 months to a ceiling dose of 25mg weekly) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral methotrexate should be used as per usual practice following national guidelines including appropriate safety monitoring.

Arm type	Experimental
Investigational medicinal product name	Clobetasol prorionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Topical clobetasol propionate 0.05% will be used once daily for one month, alternate days for 1 month then twice weekly thereon.

Investigational medicinal product name	methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral methotrexate (starting at 5mg weekly titrated upwards over 3-4 months to a ceiling dose of 25mg weekly) . Oral methotrexate should be used as per usual practice following national guidelines including appropriate safety monitoring.

Arm title	Research arm 3

Arm description:

Oral mycophenolate mofetil (starting at 500mg OD titrated upwards over 3-4 months to a ceiling dose of 3g/day) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral mycophenolate mofetil should be used as per usual practice following national guidelines including appropriate safety monitoring.

Arm type	Experimental
Investigational medicinal product name	Clobetasol prorionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Topical clobetasol propionate 0.05% will be used once daily for one month, alternate days for 1 month then twice weekly thereon.

Investigational medicinal product name	Mycophenolate mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

: Oral mycophenolate mofetil (starting at 500mg OD titrated upwards over 3-4 months to a ceiling dose of 3g/day) . Oral mycophenolate mofetil should be used as per usual practice following national

guidelines including appropriate safety monitoring

Number of subjects in period 1	Control group	Research arm 1	Research arm 2
Started	5	6	4
Completed	3	4	3
Not completed	2	2	1
Adverse event, non-fatal	-	-	-
Lost to follow-up	1	1	-
failed to start treatment	-	-	1
Lack of efficacy	1	1	-

Number of subjects in period 1	Research arm 3
Started	5
Completed	2
Not completed	3
Adverse event, non-fatal	2
Lost to follow-up	-
failed to start treatment	1
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Control group
Reporting group description:	
standard care of topical clobetasol propionate 0.05% plus a short course of oral prednisolone. N.B Topical clobetasol propionate 0.05% will be used once daily for one month, alternate days for 1 month then twice weekly thereon. This is in conjunction with an initial reducing course of oral prednisolone (20mg per day to reduce by 5mg per week over 4 weeks until stop (i.e. 20mg/day for 1 week, then 15mg/day for 1 week, then 10mg/day for 1 week, then 5mg/day for 1 week then stop)	
Reporting group title	Research arm 1
Reporting group description:	
Oral hydroxychloroquine (up to 200mg twice daily) PLUS topical clobetasol propionate 0.05%% in the same regimen as in the control group. The exact dose will be decided by the treating physician according to clinical requirement. Oral hydroxychloroquine shoRuld be used as per usual practice following national guidelines including appropriate safety monitoring.	
Reporting group title	Research arm 2
Reporting group description:	
Oral methotrexate (starting at 5mg weekly titrated upwards over 3-4 months to a ceiling dose of 25mg weekly) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral methotrexate should be used as per usual practice following national guidelines including appropriate safety monitoring.	
Reporting group title	Research arm 3
Reporting group description:	
Oral mycophenolate mofetil (starting at 500mg OD titrated upwards over 3-4 months to a ceiling dose of 3g/day) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral mycophenolate mofetil should be used as per usual practice following national guidelines including appropriate safety monitoring.	

Reporting group values	Control group	Research arm 1	Research arm 2
Number of subjects	5	6	4
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)	5	6	4
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	6	4
Male	0	0	0

Reporting group values	Research arm 3	Total	
Number of subjects	5	20	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	5	20	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	5	20	
Male	0	0	

End points

End points reporting groups

Reporting group title	Control group

Reporting group description:

standard care of topical clobetasol propionate 0.05% plus a short course of oral prednisolone. N.B Topical clobetasol propionate 0.05% will be used once daily for one month, alternate days for 1 month then twice weekly thereon. This is in conjunction with an initial reducing course of oral prednisolone (20mg per day to reduce by 5mg per week over 4 weeks until stop (i.e. 20mg/day for 1 week, then 15mg/day for 1 week, then 10mg/day for 1 week, then 5mg/day for 1 week then stop)

Reporting group title	Research arm 1

Reporting group description:

Oral hydroxychloroquine (up to 200mg twice daily) PLUS topical clobetasol propionate 0.05%% in the same regimen as in the control group. The exact dose will be decided by the treating physician according to clinical requirement. Oral hydroxychloroquine shoRuld be used as per usual practice following national guidelines including appropriate safety monitoring.

Reporting group title	Research arm 2

Reporting group description:

Oral methotrexate (starting at 5mg weekly titrated upwards over 3-4 months to a ceiling dose of 25mg weekly) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral methotrexate should be used as per usual practice following national guidelines including appropriate safety monitoring.

Reporting group title	Research arm 3

Reporting group description:

Oral mycophenolate mofetil (starting at 500mg OD titrated upwards over 3-4 months to a ceiling dose of 3g/day) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral mycophenolate mofetil should be used as per usual practice following national guidelines including appropriate safety monitoring.

Primary: treatment success

End point title	treatment success[1]

End point description:

- Patient Global Assessment of disease severity of 0 or 1 on a 4-point scale

End point type	Primary

End point timeframe:

6 months treatment period

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: Number of recruits too low to warrant statistical analyses

End point values	Control group	Research arm 1	Research arm 2	Research arm 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	4	4
Units: percent				
number (not applicable)	5	6	3	4

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in soreness

End point title	Reduction in soreness

End point description:

Numbers of participants who reported a reduction in skin soreness

End point type	Secondary

End point timeframe:

Assessed at 6 months treatment

End point values	Control group	Research arm 1	Research arm 2	Research arm 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	3	4
Units: whole numbers	0	1	0	4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or

Adverse event reporting additional description:

All serious adverse events will be recorded and reported to the MHRA and REC as part of the annual reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Control

Reporting group description:

All participants

Reporting group title	Research arm 2

Reporting group description:

Oral methotrexate (starting at 5mg weekly titrated upwards over 3-4 months to a ceiling dose of 25mg weekly) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral methotrexate should be used as per usual practice following national guidelines including appropriate safety monitoring.

Reporting group title	Research arm 1

Reporting group description:

Oral hydroxychloroquine (up to 200mg twice daily) PLUS topical clobetasol propionate 0.05%% in the same regimen as in the control group. The exact dose will be decided by the treating physician according to clinical requirement. Oral hydroxychloroquine should be used as per usual practice following national guidelines including appropriate safety monitoring.

Reporting group title	Research arm 3

Reporting group description:

Oral mycophenolate mofetil (starting at 500mg OD titrated upwards over 3-4 months to a ceiling dose of 3g/day) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral mycophenolate mofetil should be used as per usual practice following national guidelines including appropriate safety monitoring.

Serious adverse events	Control	Research arm 2	Research arm 1
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Research arm 3		
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Control	Research arm 2	Research arm 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
Skin and subcutaneous tissue disorders			
Inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	0	6

Non-serious adverse events	Research arm 3		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
Skin and subcutaneous tissue disorders			
Inflammation			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	4		

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.

Due to the small number of participants, clinical results are reported descriptively.

Notes: