Clinical trial results:
Local Oestrogen Treatment in Postmenopausal Women Undergoing Pelvic Organ Prolapse Surgery (LOTUS) - Feasibility Study

Summary

EudraCT number	2014-000179-18
Trial protocol	GB
Global end of trial date	01 September 2017

Results information

Result version number	v1 (current)
This version publication date	29 August 2019
First version publication date	29 August 2019

Trial information

Trial identification

Sponsor protocol code	RG_13-322

Additional study identifiers

ISRCTN number	ISRCTN46661996
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	MHRA: 21761/0318/001-0001

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Aston Webb Building, Birmingham, United Kingdom, B15 2TT
Public contact	Mr Sean Jennings, University of Birmingham, 0121 4158011, researchgovernance@contacts.bham.ac.uk
Scientific contact	Dr Pallavi Latthe , Birmingham Women’s Hospital, 0121 627 2672, platthe@nhs.net
Sponsor organisation name	Birmingham Women's NHS Foundation Trust
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TG
Public contact	Kelly Hard, Birmingham Women's NHS Foundation Trust, kellyhard@nhs.net
Scientific contact	Dr Pallavi Latthe, Birmingham Women's Hospital, 0121 627 2672, platthe@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	30 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2017
Global end of trial reached?	Yes
Global end of trial date	01 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the feasibility study is to find out if an appropriately powered randomised controlled trial can be realistically undertaken. The feasibility study will also allow the research team to identify any barriers to recruitment and compliance, and fine tune study procedures such as data collection and prescription of the study treatments.
The aim of the definitive study would be to test the hypothesis that vaginal oestrogen treatment of postmenopausal women undergoing pelvic floor repair surgery leads to improved patient reported outcomes in relation to urinary, bowel, sexual function and prolapse related quality of life (QoL).
Feasibility study specific objectives:
1.To obtain estimates for important aspects of the protocol to allow development of a definitive trial
2.To derive real- time data on the design aspects of the study
I.Proportion of eligible women of those screened
II.Proportion of eligible women randomised
III.Attrition rates
IV.Compliance with treatment

Protection of trial subjects:

We ensure that all staff are GCP trained and will only grant access to allow staff at site to become involved in the trial if their GCP is in date.
It is imperative that all investigators and staff at the sites have a thorough understanding of anticipated adverse events and the reporting process of these events as it is their responsibility to notify adverse events and SAE's to the Trial Office and for the Sponsor, or designated delegate, to report to the regulatory authority and ethics committee. For each SAE, the following information will be collected, from the gynaecologist, treating doctor or woman herself.
SmPC updates are checked monthly and any changes circulated to sites and pharmacy. The patient Information Sheet contained the details of the Patient Advice and Liaison Service (PALS) for the individual sites.

Background therapy:

Prolapse may be associated with weakening or atrophy of the genital tract. Oestrogen deficiency secondary to menopause results in weakening of the supporting ligaments of the pelvic organs and the pelvic floor muscles worsening the symptoms of prolapse. The vagina also contains oestrogen receptors and is sensitive to changes in circulating levels of oestrogen. Low oestradiol levels after the menopause lead to reduced vascularity of the tissues, along with a decrease in the glycogen content of epithelial cells. This in turn, leads to a fall in lactobacilli content and an increase in pH, encouraging the growth of certain bacteria, including coliforms. 9This may lead to overcolonization of the vagina, irritation and discharge. A decrease in oestrogen levels also results in atrophy of the vaginal epithelium, with more parabasal cells and fewer superficial cells seen on cytology. Associated symptoms include vaginal dryness, soreness, dyspareunia, dysuria or urinary urgency.
Oestrogen treatment can be used to reduce thinning of the vaginal and pelvic tissues. This may help to reduce or prevent the symptoms of prolapse, or may be used to make other prolapse treatments work better. The different preparations of topical hormone replacement therapy (HRT) (creams, pessaries, tablets and the estradiol vaginal ring all appear equally effective for treating vaginal atrophy but the evidence on their effectiveness in reducing symptoms related to prolapse or indeed reducing the risk of recurrence of prolapse postoperatively is non-existent.

Evidence for comparator:

Participants will be randomised individually into the study in an equal 1:1 ratio. A 'minimisation'

procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables.
Multicentre feasibility open label trial comparing vaginal low-dose oestrogen with no treatment, in 100 consenting postmenopausal women who are planning to undergo POP surgery. They will be randomly allocated to:
Intervention group (Group A): This will comprise of 6 weeks course of oestradiol 10 µg preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then 10µg oestradiol per vaginum twice weekly from 6-26 weeks postoperatively.
Comparison group (Group B) will receive no vaginal oestrogen treatment

Actual start date of recruitment	01 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	42
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

100 women were recruited to the trial between July 2015 to August 2016. Women were recruited from six UK centres with equal numbers in both the pessary group and the no treatment group.

Pre-assignment

Screening details:

The trial approached 325 women with a POP and wanting surgery and were screened for eligibility, with 157 found to be eligible . Of these screened 100 women were randomised over a 13-month period (July 2015 to August 2016). Of the 100 randomised women, 85 ultimately had surgery. Of the other 15, 6 could not have surgery due to health issues.

Pre-assignment period milestones

Number of subjects started	100
Number of subjects completed	100

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	Oestradiol 10 µg

Arm description:

Intervention group (Group A): This will comprise of 6 weeks course of oestradiol 10 µg preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then 10µg oestradiol per vaginum twice weekly from 6-26 weeks postoperatively.

Arm type	Experimental
Investigational medicinal product name	Vagifem
Investigational medicinal product code	PL 04668/0237
Other name	
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

6 weeks course of oestradiol 10 µg preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then 10µg oestradiol per vaginum twice weekly from 6-26 weeks postoperatively.

Arm title	Placebo

Arm description:

Matched placebo Intervention group (Group B): : This will comprise of 6 weeks course of pessary preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then twice weekly from 6-26 weeks postoperatively.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:
10 mg

Number of subjects in period 1	Oestradiol 10 µg	Placebo
Started	50	50
Completed	50	50

Baseline characteristics

Reporting groups	
Reporting group title	Oestradiol 10 µg
Reporting group description:	
Intervention group (Group A): This will comprise of 6 weeks course of oestradiol 10 µg preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then 10µg oestradiol per vaginum twice weekly from 6-26 weeks postoperatively.	
Reporting group title	Placebo
Reporting group description:	
Matched placebo Intervention group (Group B): : This will comprise of 6 weeks course of pessary preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then twice weekly from 6-26 weeks postoperatively.	

Reporting group values	Oestradiol 10 µg	Placebo	Total
Number of subjects	50	50	100
Age categorical			
Age category for the trial is 16-99 years of age.			
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)	21	21	42
From 65-84 years	29	29	58
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	65.7	65.9	
standard deviation	± 8.2	± 8.4	-
Gender categorical			
All female participants			
Units: Subjects			
Female	50	50	100
Ethnicity			
Units: Subjects			
White	45	43	88
Asian	2	3	5
Black	3	1	4
Mixed	0	2	2
Chinese	0	0	0
Other ethnic group	0	1	1
Not stated	0	0	0
Parity			
Units: Subjects			
<=2	27	26	53
>2	23	24	47

Maximum stage of prolapse Units: Subjects			
One	7	7	14
Two	23	23	46
Three/Four	20	20	40
Hysterectomy Units: Subjects			
Yes	12	8	20
No	38	42	80
Treatment for over active bladder Units: Subjects			
Yes	0	0	0
No	50	50	100
Vaginal pessary/ring currently in place Units: Subjects			
Yes	5	8	13
No	45	42	87
Concomitant continence surgery Units: Subjects			
Yes	2	3	5
No	48	47	95
Physiotherapy treatment for prolapse/Urinary incontinence in last 12 months Units: Subjects			
Yes	8	10	18
No	42	40	82
Previous operation for prolapse Units: Subjects			
Yes	4	4	8
No	46	46	92
Drug treatment for urinary incontinence Units: Subjects			
Yes	0	4	4
No	50	46	96
BMI Units: mg/k2			
arithmetic mean	28.1	28.2	
standard deviation	± 5.1	± 7	-
Spontaneous vaginal delivery Units: subjects			
median	2	2	
inter-quartile range (Q1-Q3)	2 to 3	2 to 4	-
Caesareans Units: Subjects			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 0	-
Anterior Units: Number of repairs			
median	1	1	
inter-quartile range (Q1-Q3)	1 to 1	1 to 1	-
Posterior			

Units: Number of repairs			
median	1	1	
inter-quartile range (Q1-Q3)	1 to 1	1 to 1	-

Subject analysis sets

Subject analysis set title	Period 1
Subject analysis set type	Full analysis

Subject analysis set description:

Baseline set

Reporting group values	Period 1		
Number of subjects	100		
Age categorical			
Age category for the trial is 16-99 years of age.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	42		
From 65-84 years	58		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	65.8		
standard deviation	± 8.3		
Gender categorical			
All female participants			
Units: Subjects			
Female	100		
Ethnicity			
Units: Subjects			
White	88		
Asian	5		
Black	4		
Mixed	2		
Chinese	0		
Other ethnic group	1		
Not stated	0		
Parity			
Units: Subjects			
<=2	53		
>2	47		
Maximum stage of prolapse			
Units: Subjects			
One	14		

Two	64		
Three/Four	40		
Hysterectomy Units: Subjects			
Yes	20		
No	80		
Treatment for over active bladder Units: Subjects			
Yes	0		
No	100		
Vaginal pessary/ring currently in place Units: Subjects			
Yes	13		
No	87		
Concomitant continence surgery Units: Subjects			
Yes	5		
No	95		
Physiotherapy treatment for prolapse/Urinary incontinence in last 12 months Units: Subjects			
Yes	18		
No	82		
Previous operation for prolapse Units: Subjects			
Yes	8		
No	92		
Drug treatment for urinary incontinence Units: Subjects			
Yes	4		
No	96		
BMI Units: mg/k2			
arithmetic mean	28.2		
standard deviation	± 5.5		
Spontaneous vaginal delivery Units: subjects			
median	2		
inter-quartile range (Q1-Q3)	2 to 3		
Caesareans Units: Subjects			
median	0		
inter-quartile range (Q1-Q3)	0 to 0		
Anterior Units: Number of repairs			
median	1		
inter-quartile range (Q1-Q3)	1 to 1		
Posterior Units: Number of repairs			
median	1		
inter-quartile range (Q1-Q3)	1 to 1		

End points

End points reporting groups

Reporting group title	Oestradiol 10 µg
Reporting group description:	
Intervention group (Group A): This will comprise of 6 weeks course of oestradiol 10 µg preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then 10µg oestradiol per vaginum twice weekly from 6-26 weeks postoperatively.	
Reporting group title	Placebo
Reporting group description:	
Matched placebo Intervention group (Group B): : This will comprise of 6 weeks course of pessary preoperatively per vaginum (once daily for 2 weeks followed by twice weekly for four weeks) and then twice weekly from 6-26 weeks postoperatively.	
Subject analysis set title	Period 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Baseline set	

Primary: Primary PFDI-SF20 at 6 months

End point title	Primary PFDI-SF20 at 6 months
End point description:	
End point type	Primary
End point timeframe:	
From Randomisation to completion of PFDI-SF20 at 6 months	

End point values	Oestradiol 10 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	41		
Units: Subjects				
arithmetic mean (standard deviation)				
Numbers	45.4 (± 43.8)	45.0 (± 37.1)		

Statistical analyses

Statistical analysis title	linear regression model
Comparison groups	Placebo v Oestradiol 10 µg
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	17.2

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Randomisation to completion of follow up

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Oestrogen Group
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no adverse events. Just 4 serious adverse events.

Serious adverse events	Oestrogen Group	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 50 (4.00%)	2 / 50 (4.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Pancreatic carcinoma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
High Temperature			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding time abnormal	Additional description: Patient bleeding heavily and admitted to hospital for antibiotics.		

subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	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	Oestrogen Group	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	

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.

N/A

Notes: