Clinical trial results:
PRE-EMPT: Preventing Recurrence of Endometriosis by Means of long acting Protestogen Therapy

Summary

EudraCT number	2013-001984-21
Trial protocol	GB
Global end of trial date	31 May 2023

Results information

Result version number	v1 (current)
This version publication date	14 February 2024
First version publication date	14 February 2024

Trial information

Trial identification

Sponsor protocol code	3/013/13

Additional study identifiers

ISRCTN number	ISRCTN97865475
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Aberdeen and NHS Grampian
Sponsor organisation address	Aberdeen Royal Infirmary, Cornhill Road, Aberdeen , United Kingdom, AB25 2ZD
Public contact	Dr Gail Holland, University of Aberdeen & NHS Grampian, 44 01224 551123, G.Holland@abdn.ac.uk
Scientific contact	Dr Gail Holland, University of Aberdeen & NHS Grampian, 44 01224 551123, G.Holland@abdn.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	31 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2023
Global end of trial reached?	Yes
Global end of trial date	31 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main study principal objective:
To compare, in women undergoing conservative surgery for pain due to endometriosis, the effectiveness of some or all of the following four post-surgical treatment options in controlling the recurrence of symptoms and improving quality of life: 1) no treatment 2) levonorgestrel-releasing intra-uterine System (LNG IUS) 3) three monthly depot medroxyprogesterone acetate injections (DMPA) 4) the combined oral contraceptive pill (COC), dependent on the groups carried forward from the pilot.

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. The patient Information Sheet contained the details of the Patient Advice and Liaison Service (PALS) for the individual sites. The Data Monitoring & Ethics Committee (DMEC) are assigned to review overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis.

Background therapy: -

Evidence for comparator:

Randomisation occurred either intra-operatively, or immediately post-operatively, according to the randomisation options and the intention of the investigator. The stage of endometriosis, the need for additional surgery and the extent of the surgical excision or ablation of the endometriosis are the remaining eligibility criteria and stratification variables that could only established at laparoscopy.

A 'minimisation' procedure using a computer-based algorithm was used to avoid chance imbalances in important stratification variables.
- Stage of endometriosis (using Classification of the American Society of Reproductive Medicine): I (minimal) II (mild) versus III (moderate)/ IV (severe)
- Extent of excision of endometriosis: complete versus incomplete, as judged by the surgeon at the time of conservative surgery
- Age in years:<35 versus >=35
- Selection of LNG-IUS or DMPA if randomised to LARC
- Whether selection of LARC was due to patient preference or not
- Centre, to balance for experience of the gynaecologist

If the LARC needed to be randomly allocated prior to LARC v COCP allocation this was completed using a random blocked list (variable length) incorporated into the computer-based algorithm.

Actual start date of recruitment	01 January 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: 405
Worldwide total number of subjects	405
EEA total number of subjects	0

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)	5
Adults (18-64 years)	400
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

PRE- EMPT participants were recruited from the gynaecological, out-patient clinics of participating centres, fitting around their current service provision. Long term medical treatment i.e. repeat COCP prescriptions and DMPA injections, were delivered by the participants GP or sexual health clinics, as per current practice.

Pre-assignment

Screening details:

In women aged 16-46 years presenting with pelvic pain associated with endometriosis, anatomical location, severity of the disease and degree of involvement of neighbouring organs can all show a remarkable degree of variation.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	LARC

Arm description:

Long-acting reversible contraception

Arm type	Active comparator
Investigational medicinal product name	Long-acting reversible contraception: LNG-IUS or DMPA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Vaginal use

Dosage and administration details:

Implant

Arm title	COCP

Arm description:

Combined oral contraceptive pill

Arm type	Active comparator
Investigational medicinal product name	Combined oral contraceptive pill
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30mcg ethinylestradiol and 150 mcg levonorgestrel e.g. Microgynon-30 or Rigevidon.

Number of subjects in period 1	LARC	COCP
Started	205	200
Completed	205	200

Period 2	
Period 2 title	3 Years
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	LARC

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Long-acting reversible contraception: LNG-IUS or DMPA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Vaginal use

Dosage and administration details:

Implant

Arm title	COCP

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Combined oral contraceptive pill
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30mcg ethinylestradiol and 150 mcg levonorgestrel e.g. Microgynon-30 or Rigevidon.

Number of subjects in period 2	LARC	COCP
Started	205	200
6 Months	176	173
1 Year	176	171
2 Year	174	165

Completed	173	164
Not completed	32	36
Lost to follow-up	32	36

Baseline characteristics

Reporting groups	
Reporting group title	LARC
Reporting group description: Long-acting reversible contraception	
Reporting group title	COCP
Reporting group description: Combined oral contraceptive pill	

Reporting group values	LARC	COCP	Total
Number of subjects	205	200	405
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)	3	2	5
Adults (18-64 years)	202	198	400
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	29.6	29.3	
standard deviation	± 6.7	± 6.6	-
Gender categorical Units: Subjects			
Female	205	200	405
Male	0	0	0

End points

End points reporting groups

Reporting group title	LARC
Reporting group description: Long-acting reversible contraception	
Reporting group title	COCP
Reporting group description: Combined oral contraceptive pill	
Reporting group title	LARC
Reporting group description: -	
Reporting group title	COCP
Reporting group description: -	
Subject analysis set title	LARC Baseline
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at Baseline	
Subject analysis set title	LARC 6 Months
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at 6 Months	
Subject analysis set title	LARC 1 Year
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at 1 Year	
Subject analysis set title	LARC 2 Years
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at 2 Years	
Subject analysis set title	LARC 3 Years
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at 3 Years	
Subject analysis set title	COCP Baseline
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at Baseline	
Subject analysis set title	COCP 6 Months
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at 6 Months	
Subject analysis set title	COCP 1 Year
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at 1 Year	
Subject analysis set title	COCP 2 Year
Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at 2 Years	
Subject analysis set title	COCP 3 Year

Subject analysis set type	Full analysis
Subject analysis set description: Analysis population who completed at 3 Years	

Primary: Primary Outcome EHP-30 - Pain scores

End point title	Primary Outcome EHP-30 - Pain scores
End point description:	

End point type	Primary
End point timeframe: 3 Years	

End point values	LARC	COCP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	164		
Units: Pain Scores				
arithmetic mean (standard deviation)	32.9 (± 25.0)	32.9 (± 27.6)		

Statistical analyses

Statistical analysis title	Adjusted Mean Difference
Comparison groups	LARC v COCP
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	4.2

Secondary: Baseline EHP-30 - Pain scores

End point title	Baseline EHP-30 - Pain scores
End point description:	

End point type	Secondary
End point timeframe: Baseline	

End point values	LARC Baseline	COCP Baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	192		
Units: Pain Scores				
arithmetic mean (standard deviation)	56.6 (± 17.3)	55.8 (± 19.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1 Year EHP-30 - Pain scores

End point title	1 Year EHP-30 - Pain scores

End point description:

End point type	Secondary

End point timeframe:

1 Year

End point values	LARC 1 Year	COCP 1 Year		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150	153		
Units: Pain Scores				
arithmetic mean (standard deviation)	35.1 (± 26.4)	37.5 (± 25.4)		

Statistical analyses

Statistical analysis title	Adjusted Mean Difference
Comparison groups	COCP 1 Year v LARC 1 Year
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	2.9

Secondary: 2 Year EHP-30 - Pain scores

End point title	2 Year EHP-30 - Pain scores

End point description:

End point type	Secondary

End point timeframe:

2 Year

End point values	LARC 2 Years	COCP 2 Year		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	157	140		
Units: Pain Scores				
arithmetic mean (standard deviation)	32.1 (± 26.2)	33.6 (± 26.5)		

Statistical analyses

Statistical analysis title	Adjusted Mean Difference
Comparison groups	LARC 2 Years v COCP 2 Year
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	4.9

Secondary: 6 Month EHP-30 - Pain scores

End point title	6 Month EHP-30 - Pain scores

End point description:

End point type	Secondary

End point timeframe:

6 Months

End point values	LARC 6 Months	COCP 6 Months		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	162	150		
Units: Pain Scores				
arithmetic mean (standard deviation)	35.0 (± 25.6)	38.0 (± 26.4)		

Statistical analyses

Statistical analysis title	Adjusted Mean Difference
Comparison groups	LARC 6 Months v COCP 6 Months
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	3.2

Secondary: Further therapeutic surgery or second-line treatment for endometriosis over 3 years

End point title	Further therapeutic surgery or second-line treatment for endometriosis over 3 years
End point description:	
Time to further therapeutic surgery or second line treatment: HR=0.67 (95% CI: 0.44, 1.00)	
End point type	Secondary
End point timeframe:	
Over 3 years	

End point values	LARC 3 Years	COCP 3 Year		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73	97		
Units: No. of participants				
Hysterectomy	6	14		
Surgery for endometriosis	21	30		
Laparoscopy	22	28		
GnRH treatment	24	25		
Total no. of women experiencing treatment failure	50	61		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

PRE-EMPT AE reporting was conducted primarily by the participant. This was captured in the routine follow up questionnaires received during follow up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	LARC

Reporting group description:

Long-acting reversible contraception

Reporting group title	COCP

Reporting group description:

Combined oral contraceptive pill

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: No non-serious adverse events were recorded

Serious adverse events	LARC	COCP	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 205 (6.83%)	15 / 200 (7.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Bleeding time	Additional description: Patient bleed more than expected during surgery. Kept in overnight for observation . Discharged home the following day.		
subjects affected / exposed	1 / 205 (0.49%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bowel obstruction surgery	Additional description: Resection of bowel tumour		
subjects affected / exposed	0 / 205 (0.00%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laparoscopy			
subjects affected / exposed	2 / 205 (0.98%)	3 / 200 (1.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Carpal tunnel syndrome	Additional description: Patient reported to BCTU that she had surgery for Capral tunnel syndrome. No date on clinical records to supper this. Seen by Plastics who recommended decompression under local anaesthetic to relieve symptoms. Th		
subjects affected / exposed	0 / 205 (0.00%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Hyperemesis gravidarum			
subjects affected / exposed	1 / 205 (0.49%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy			
subjects affected / exposed	3 / 205 (1.46%)	3 / 200 (1.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Abdominal pain	Additional description: Admitted via A&E ,sever abdo pain & reflux. Admitted with intermittent back pan & right sided abdominal pain radiating to flank & right lilac fossa.		
subjects affected / exposed	1 / 205 (0.49%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	8 / 205 (3.90%)	4 / 200 (2.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion	Additional description: Had concussion which resulted in an overnight stay (don't know exact date) had an MRI or cat scan doesn't know which. Unable to access GP records. Patient had stopped trial med (Depo)		
subjects affected / exposed	1 / 205 (0.49%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis	Additional description: Extensive grade 4 pelvic endometriosis		
subjects affected / exposed	0 / 205 (0.00%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture	Additional description: Stress fracture left sacral		
subjects affected / exposed	0 / 205 (0.00%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Discontinued product administered	Additional description: Patient randomised to depo injection. Only had 1 dose then discontinued treatment, affected her mood adversely.		
subjects affected / exposed	1 / 205 (0.49%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 205 (0.98%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Epstein-Barr virus infection			
subjects affected / exposed	1 / 205 (0.49%)	0 / 200 (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	LARC	COCP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 205 (0.00%)	0 / 200 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2014	Updates to protocol and trial documents.
23 October 2015	Move from pilot to substantive study • Removal of no treatment arm. • Removal of qualitative study • Update protocol with change of DMC member • PIS updated with design change • Consent updated to reflect PIS • GP letter and follow-up form update
18 May 2017	Extension until 31/12/17. Introduction of vouchers for follow up participants. Addition of Levosert as additional LNG-IUS.
05 April 2018	Update to protocol and trial documents.
06 October 2020	Revision of section 6 within the protocol to reject the wording previously added exempting congenital abnormalities from SAE reporting.
02 March 2022	£25 sent to final participants on completion of follow-up form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported