Clinical trial results:
Double blind crossover randomised controlled trial comparing letrozole versus clomifene citrate for ovulation induction in women with polycystic ovarian syndrome

Summary

EudraCT number	2006-006514-15
Trial protocol	GB
Global end of trial date	30 June 2014

Results information

Result version number	v1 (current)
This version publication date	16 March 2019
First version publication date	16 March 2019
Summary attachment (see zip file)	Double-blind randomized controlled trial of letrozole versus clomiphene citrate in subfertile women with polycystic ovarian syndrome (Amer et al Hum Reprod 2017.pdf)

Trial information

Trial identification

Sponsor protocol code	RD-5103-015-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00478504
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	University Park, Nottingham, United Kingdom, NG7 2RD
Public contact	Head of Research Governance Research and Innovation, University of Nottingham , Professor Saad Amer School Of Graduate Entry Medicine University of Nottingham , +44 1332724612, saad.amer@nottingham.ac.uk
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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	19 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2014
Global end of trial reached?	Yes
Global end of trial date	30 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to assess the efficacy of letrozole as an ovulation induction agent and to test the hypothesis that letrozole will generate better pregnancy rates than treatment with the current standard agent, clomifene citrate.

Protection of trial subjects:

This was a low risk trial. All participants were given contact numbers to call any time for any concerns.

Background therapy:

Nne

Evidence for comparator:

For decades, clomiphene citrate (CC) has been the standard first line ovulation induction (OI) agent in PCOS women with 85% ovulation rates and 40% pregnancy rates. This discrepancy between ovulation and conception rates has been attributed to the peripheral antioestrogenic actions of CC on endometrium and cervix.
Letrozole, an aromatase inhibitor that reduces oestrogen synthesis, has recently been considered as a potentially better alternative to CC. In contrast to CC, letrozole is not associated with any anti-oestrogenic effects on endometrium. This is supported by recent studies reporting adequate endometrial thickness during letrozole treatment. Furthermore, unlike CC that accumulates in the body because of its long half-life (two weeks), letrozole is rapidly eliminated due to its short half-life (45 hours), leading to late follicular rise in circulating oestrogen thereby enhancing endometrial development with subsequent increase in the chances of pregnancy. The rising oestrogen levels may also result in a shorter FSH window (mimicking the physiological cycle) with subsequent mono-ovulation and a lower risk of multiple pregnancy.
A Cochrane systematic review of clinical trials comparing aromatase inhibitors versus CC concluded that the quality of evidence in the reviewed trials was low due to poor reporting of study methods and possible publication bias. None of the reviewed trials was conducted in Europe. Furthermore, the only robust trial in that review included a high proportion of markedly obese women (Body mass Index (BMI)>40kg/m2), which does not reflect clinical practice in the majority of fertility centres worldwide (Legro et al, 2014). These results are therefore neither conclusive nor generalizable. The review concluded that further research is needed to compare letrozole with CC as a primary ovulation induction (OI) agent in PCOS women.

Actual start date of recruitment	25 April 2007
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: 159
Worldwide total number of subjects	159
EEA total number of subjects	159

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)	159
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited at the fertility unit of Royal Derby Hospital between 25 April 2007 and 22 February 2013.

Pre-assignment

Screening details:

A total of 202 women with anovulatory infertility due to PCOS were screened for eligibility, of whom 159 were randomized. the remaining 43 women were excluded due to not meeting inclusion criteria (n=25), declining to participate (n=8) or conceiving before recruitment (n=10).

Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The two medicines investigated in the trial were prepared in identical capsules and provided in identical packages (as explained above). Throughout the study, the patient and the investigator remained blinded to the treatment. Investigators carrying out the monitoring, assessment of response to treatment and data analysis were kept blinded. The dispenser of the medicine kept the identifying tear-off label of each pack to allow unblinking at any time if necessary.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Clomifene

Arm description:

79 Participants allocated to clomiphene citrate

Arm type	Active comparator
Investigational medicinal product name	Clomiphene citrate
Investigational medicinal product code	
Other name	Clomifene citrate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Clomiphene citrate was given orally daily for five days in the early follicular phase from day 2 to day 6 of a spontaneous menstrual period or a withdrawal bleed induced by progestogen administration. The starting daily dose was one capsule 50 mg. Patients were monitored for ovulation by follicle tracking (using ultrasound) and measurement of serum concentration of progesterone in mid-luteal phase. If the patient did not ovulate on one capsule the dose would be increased in the second cycle to two capsules a day (i.e. 100 mg/day). Once ovulation had been achieved on a certain dose, treatment would be continued until pregnancy is achieved or for up to 6 cycles.

Arm title	Arm B: letrozole

Arm description:

80 Participants allocated to letrozole

Arm type	Experimental
Investigational medicinal product name	Letozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole was given orally daily for five days in the early follicular phase from day 2 to day 6 of a spontaneous menstrual period or a withdrawal bleed induced by progestogen administration. The starting daily dose was one capsule 2.5 mg. Patients were monitored for ovulation by follicle tracking (using ultrasound) and measurement of serum concentration of progesterone in mid-luteal phase. If the patient did not ovulate on one capsule the dose would be increased in the second cycle to two capsules a day (i.e. 5 mg/day). Once ovulation had been achieved on a certain dose, treatment would be continued until pregnancy is achieved or for up to 6 cycles.

Number of subjects in period 1	Arm A: Clomifene	Arm B: letrozole
Started	79	80
Completed	74	75
Not completed	5	5
Consent withdrawn by subject	-	2
Pregnancy	2	2
Lost to follow-up	3	1

Period 2

Period 2 title	Cross-over
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The two medicines investigated in the trial were prepared in identical capsules and provided in identical packages (as explained above). Throughout the study, the patient and the investigator remained blinded to the treatment. Investigators carrying out the monitoring, assessment of response to treatment and data analysis were kept blinded. The dispenser of the medicine kept the identifying tear-off label of each pack to allow unblinking at any time if necessary.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Clomifene

Arm description:

79 Participants allocated to clomiphene citrate

Arm type	Active comparator
Investigational medicinal product name	Clomiphene citrate
Investigational medicinal product code	
Other name	Clomifene citrate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Clomiphene citrate was given orally daily for five days in the early follicular phase from day 2 to day 6 of a spontaneous menstrual period or a withdrawal bleed induced by progestogen administration. The starting daily dose was one capsule 50 mg. Patients were monitored for ovulation by follicle tracking (using ultrasound) and measurement of serum concentration of progesterone in mid-luteal phase. If the patient did not ovulate on one capsule the dose would be increased in the second cycle to two capsules

a day (i.e. 100 mg/day). Once ovulation had been achieved on a certain dose, treatment would be continued until pregnancy is achieved or for up to 6 cycles.

Arm title	Arm B: letrozole
Arm description: 80 Participants allocated to letrozole	
Arm type	Experimental
Investigational medicinal product name	Letozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole was given orally daily for five days in the early follicular phase from day 2 to day 6 of a spontaneous menstrual period or a withdrawal bleed induced by progestogen administration. The starting daily dose was one capsule 2.5 mg. Patients were monitored for ovulation by follicle tracking (using ultrasound) and measurement of serum concentration of progesterone in mid-luteal phase. If the patient did not ovulate on one capsule the dose would be increased in the second cycle to two capsules a day (i.e. 5 mg/day). Once ovulation had been achieved on a certain dose, treatment would be continued until pregnancy is achieved or for up to 6 cycles.

Number of subjects in period 2	Arm A: Clomifene	Arm B: letrozole
Started	74	75
Completed	74	75

Baseline characteristics

Reporting groups

Reporting group title	Randomisation

Reporting group description: -

Reporting group values	Randomisation	Total	
Number of subjects	159	159	
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)	159	159	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	159	159	
Male	0	0	

Subject analysis sets

Subject analysis set title	Arm A: Clomifene
Subject analysis set type	Full analysis

Subject analysis set description:

Patients started on Clomifene then crossed over to Letrozole

Subject analysis set title	Arm B: Letrozole
Subject analysis set type	Full analysis

Subject analysis set description:

Patients started on Letrozole then crossed over to Clomifene

Reporting group values	Arm A: Clomifene	Arm B: Letrozole	
Number of subjects	74	75	
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)	74	75	

From 65-84 years	0	0	
85 years and over	0	0	

Gender categorical Units: Subjects			
Female	74	75	
Male	0	0	

End points

End points reporting groups	
Reporting group title	Arm A: Clomifene
Reporting group description: 79 Participants allocated to clomiphene citrate	
Reporting group title	Arm B: letrozole
Reporting group description: 80 Participants allocated to letrozole	
Reporting group title	Arm A: Clomifene
Reporting group description: 79 Participants allocated to clomiphene citrate	
Reporting group title	Arm B: letrozole
Reporting group description: 80 Participants allocated to letrozole	
Subject analysis set title	Arm A: Clomifene
Subject analysis set type	Full analysis
Subject analysis set description: Patients started on Clomifene then crossed over to Letrozole	
Subject analysis set title	Arm B: Letrozole
Subject analysis set type	Full analysis
Subject analysis set description: Patients started on Letrozole then crossed over to Clomifene	

Primary: Pregnancy rate	
End point title	Pregnancy rate
End point description: Pregnancy achieved	
End point type	Primary
End point timeframe: At any time in the trial	

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	75		
Units: Number	32	47		

Statistical analyses

Statistical analysis title	Difference in pregnancy rate
Statistical analysis description: Absolute difference in pregnancy rate between arm A and arm B	
Comparison groups	Arm B: Letrozole v Arm A: Clomifene

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.018
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.34
Variability estimate	Standard error of the mean

Secondary: Ovulation rate

End point title	Ovulation rate

End point description:

End point type	Secondary

End point timeframe:

At any time in trial

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	75		
Units: Number	60	66		

Statistical analyses

Statistical analysis title	Difference in ovulation rate

Statistical analysis description:

Absolute difference in ovulation rate between the two arms

Comparison groups	Arm A: Clomifene v Arm B: Letrozole
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.173
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.19
Variability estimate	Standard error of the mean

Secondary: Live birth

End point title	Live birth
End point description:	
End point type	Secondary
End point timeframe:	
At end of trial treatment	

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	75		
Units: Number	26	37		

Statistical analyses

Statistical analysis title	Difference in live birth
Statistical analysis description:	
Absolute difference in live birth rate between the two arms	
Comparison groups	Arm A: Clomifene v Arm B: Letrozole
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.079
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.29
Variability estimate	Standard error of the mean

Secondary: Pregnancy per ovulating patient	
End point title	Pregnancy per ovulating patient
End point description:	

End point type	Secondary
End point timeframe:	
At end of trial treatment	

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	66		
Units: Number	32	47		

Statistical analyses

Statistical analysis title	Difference in pregnancy rate per ovulating patien
Statistical analysis description:	
Absolute difference in pregnancy rate per patient who achieved ovulation	
Comparison groups	Arm A: Clomifene v Arm B: Letrozole
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.038
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.3
Variability estimate	Standard error of the mean

Secondary: Pregnancy per cycle	
End point title	Pregnancy per cycle
End point description:	

End point type	Secondary
End point timeframe:	
Any time in trial	

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	278	261		
Units: Number	34	49		

Statistical analyses

Statistical analysis title	Difference in pregnancy rate per cycle
Comparison groups	Arm A: Clomifene v Arm B: Letrozole
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.036
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.13
Variability estimate	Standard error of the mean

Secondary: Live birth per cycle

End point title	Live birth per cycle
End point description:	

End point type	Secondary
End point timeframe:	
At end of trial	

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	278	261		
Units: Number	28	39		

Statistical analyses

Statistical analysis title	Difference in live birth rate per cycle
Statistical analysis description:	
Absolute difference in live birth rate per cycle between the two arms	
Comparison groups	Arm B: Letrozole v Arm A: Clomifene
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.087
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.11
Variability estimate	Standard error of the mean

Secondary: Ovulation per cycle

End point title	Ovulation per cycle
End point description:	
End point type	Secondary
End point timeframe:	
Any time in trial	

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	278	261		
Units: Number	187	196		

Statistical analyses

Statistical analysis title	Difference in ovulation rate per cycle
Comparison groups	Arm A: Clomifene v Arm B: Letrozole

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.045
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.15
Variability estimate	Standard error of the mean

Secondary: Mono-ovulation

End point title	Mono-ovulation
End point description:	
Ovulation in cycles with only one follicle developed	
End point type	Secondary
End point timeframe:	
Any time in trial	

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77	94		
Units: number	64	80		

Statistical analyses

Statistical analysis title	Difference in ovulation from one follicle
Statistical analysis description:	
Absolute difference in ovulation where only one follicle present between the two arms	
Comparison groups	Arm A: Clomifene v Arm B: Letrozole
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.723
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.09
Variability estimate	Standard error of the mean

Secondary: Pregnancy outcome and complications

End point title	Pregnancy outcome and complications

End point description:

End point type	Secondary

End point timeframe:

At end of pregnancy/trial

End point values	Arm A: Clomifene	Arm B: Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	75	79		
Units: Number				
Miscarriage	6	9		
Ectopic	0	1		
Preterm	2	4		
Term	35	26		
Twins	0	3		
Foetal abnormalites	0	0		
Foetal complications	3	3		
IUGR	2	2		
Macrosomia	0	1		
Malpresentation	1	0		
Matenrla complications	7	2		
IOL	13	9		
CS	7	7		
Delivery Complications	1	0		
Neonatal hypoglycaemia	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout trial	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	1.0
Reporting groups	
Reporting group title	Arm A: Clomifene
Reporting group description: 79 Participants allocated to clomiphene citrate	
Reporting group title	Arm B: letrozole
Reporting group description: 80 Participants allocated to letrozole	

Serious adverse events	Arm A: Clomifene	Arm B: letrozole	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 79 (2.53%)	1 / 80 (1.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Haemorrhagic cyst			
subjects affected / exposed	1 / 79 (1.27%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 80 (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: 1 %

Non-serious adverse events	Arm A: Clomifene	Arm B: letrozole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 79 (13.92%)	12 / 80 (15.00%)	

Pregnancy, puerperium and perinatal conditions			
cyst formation			
subjects affected / exposed	3 / 79 (3.80%)	3 / 80 (3.75%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
hot hands			
subjects affected / exposed	0 / 79 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
heavy legs			
subjects affected / exposed	0 / 79 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Miscellaneous			
subjects affected / exposed	5 / 79 (6.33%)	5 / 80 (6.25%)	
occurrences (all)	5	5	
Gastrointestinal disorders			
Diarrhoea, nausea and vomiting			
subjects affected / exposed	0 / 79 (0.00%)	2 / 80 (2.50%)	
occurrences (all)	0	2	
Endocrine disorders			
Hot flushes and headaches			
subjects affected / exposed	3 / 79 (3.80%)	0 / 80 (0.00%)	
occurrences (all)	3	0	

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

None reported