Clinical trial results:
The use of Metformin and Gonadotrophin Releasing Hormone Antagonist for the treatment of women with Polycystic Ovary Syndrome undergoing In-vitro Fertilisation-Embryo Transfer.

Summary

EudraCT number	2009-010952-81
Trial protocol	GB
Global end of trial date	01 July 2014

Results information

Result version number	v1 (current)
This version publication date	10 February 2018
First version publication date	10 February 2018

Trial information

Trial identification

Sponsor protocol code	OG08/8802

Additional study identifiers

ISRCTN number	ISRCTN21199799
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Leeds Teaching Hospitals NHS Trust
Sponsor organisation address	Beckett Street, Leeds, United Kingdom, LS9 7TF
Public contact	Doctor Susie Nicholas, Leeds Centre of Reproductive Medicine Seacroft Hospital Leeds LS14 6UH, 0044 1132063111,
Scientific contact	Doctor Susie Nicholas, Leeds Centre of Reproductive Medicine Seacroft Hospital Leeds LS14 6UH, 0044 1132063111,

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	01 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The prinicpal research objective is to determine if the administration of the drug metformin to women with polycystic ovary syndrome who are undergoing IVF treatment following the short GnRH antagonist treatment protocol reduces the incidence of moderate to severe ovarian hyperstimulation syndrome (OHHS) (i.e. Does metformin reduce the risk of OHSS in this group?).

Protection of trial subjects:

Monitored during stimulation phase and for OHSS, and live birth outcome.

Background therapy:

Stimulation drugs including Gonal F and puregon and GNRH antagonist(orgalutron/cetrotide).

Evidence for comparator:

Comparing if Metformin reduced risk of OHSS against a placebo. Evidence available that Metformin reduces risk of OHSS in long GNRH agonist. Also has effect on clinical pregnancy rates in IVF treatments. No other medication has same safety profile as this for use in early pregnancy.

Actual start date of recruitment	30 October 2009
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: 153
Worldwide total number of subjects	153
EEA total number of subjects	153

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)	153

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruited from IVF clinic waiting list between October 2009 and June 2014 (One year where recruitment was paused with change over of principal investigator)

Pre-assignment

Screening details:

All women on waiting list were screened for inclusion - those eligible fulfilled the Rotterdam criteria plus BMI and age criteria. 169 women were enrolled - 153 started medication . 16 didn't start for a number of reasons including pregnancy, no longer eligible or withdrew consent

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Randomisation by the hospital pharmacy using random permuted blocks method with a 50:50 allocation ratio

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin

Arm description:

Those patients allocated metformin treatment

Arm type	Active comparator
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule twice a day

Arm title	Placebo

Arm description:

Those allocated placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule twice a day

Number of subjects in period 1	Metformin	Placebo
Started	77	76
Completed	77	76

Baseline characteristics

Reporting groups	
Reporting group title	Metformin
Reporting group description:	
Those patients allocated metformin treatment	
Reporting group title	Placebo
Reporting group description:	
Those allocated placebo	

Reporting group values	Metformin	Placebo	Total
Number of subjects	77	76	153
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)	77	76	153
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	77	76	153
Male	0	0	0

End points

End points reporting groups	
Reporting group title	Metformin
Reporting group description:	
Those patients allocated metformin treatment	
Reporting group title	Placebo
Reporting group description:	
Those allocated placebo	

Primary: Incidence of moderate-severe OHSS with 6 weeks of cycle	
End point title	Incidence of moderate-severe OHSS with 6 weeks of cycle
End point description:	
End point type	Primary
End point timeframe:	
6 weeks from starting IVF cycle	

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	76		
Units: subjects	12	9		

Statistical analyses

Statistical analysis title	OHSS rate
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	153
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 1-sided
Parameter estimate	Odds ratio (OR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	3.49
Variability estimate	Standard deviation

Secondary: Clinical pregnancy rate

End point title	Clinical pregnancy rate
End point description:	
When fetal heart beat was seen on 7 week pregnancy ultrasound	
End point type	Secondary
End point timeframe:	
start of trial to 7 weeks after final treatment date of last patient enrolled	

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	76		
Units: pregnancies				
Pregnant	22	37		
Not pregnant	55	39		

Statistical analyses

Statistical analysis title	Clinical pregnancy rate
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Chi-squared corrected
Parameter estimate	Mean difference (net)

Secondary: Number of oocytes collected

End point title	Number of oocytes collected
End point description:	
total number of oocytes collected during treatment	
End point type	Secondary
End point timeframe:	
start of trial to last patient's egg collection	

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	76		
Units: egg number	14	15		

Statistical analyses

Statistical analysis title	Oocyte number
Statistical analysis description: average number of oocytes per patient	
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	153
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)

Secondary: Number of patients with good day 3 embryos

End point title	Number of patients with good day 3 embryos
End point description:	
End point type	Secondary
End point timeframe: start of trial to last clinical treatment of last patient	

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	76		
Units: embryo number				
number (not applicable)	47.1	52.3		

Statistical analyses

Statistical analysis title	Good day 3 embryos
Comparison groups	Metformin v Placebo

Number of subjects included in analysis	153
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 1-sided
Parameter estimate	Mean difference (net)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Within 6 weeks of starting IVF cycle plus then until birth of child (9 months)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	1
Reporting groups	
Reporting group title	Adverse incidents - OHSS
Reporting group description: -	
Reporting group title	Cyst admission
Reporting group description: those with hospital admission die to cyst	

Serious adverse events	Adverse incidents - OHSS	Cyst admission	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 153 (4.58%)	1 / 153 (0.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
moderate to severe OHSS			
subjects affected / exposed	7 / 153 (4.58%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	7 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	7 / 153 (4.58%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	7 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Adverse incidents - OHSS	Cyst admission	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 153 (4.58%)	0 / 153 (0.00%)	

Reproductive system and breast disorders			
OHSS			
subjects affected / exposed	7 / 153 (4.58%)	0 / 153 (0.00%)	
occurrences (all)	7	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2013	A number of amendments occurred which involved updating clinical information and protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 January 2012	due to change in principal investigator - lapse in recruitment and updating of clinical information	30 August 2012

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27816925