



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 principal 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 (OHSS) (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

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|-----------------|-----------------------------|
| 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)

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|-----------------|----------------|
| 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>