



## Clinical trial results:

### A Multi-Centre, Two-Arm, Interventional, Phase IV Study to Evaluate Tailoring of Recombinant FSH Treatment in Subjects With Chronic Anovulation Using the Gonal-f® Prefilled Pen in Women Undergoing Ovulation Induction

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-003227-38 |
| Trial protocol           | GB IE          |
| Global end of trial date | 23 July 2015   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 28 July 2016 |
| First version publication date | 28 July 2016 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | EMR700623_535 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01871532 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Merck KGaA  |
| Sponsor organisation address | Frankfurter Strasse 250, Darmstadt, Germany, 64293                                  |
| Public contact               | Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com |
| Scientific contact           | Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com |

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                       | 25 March 2014 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 23 July 2015  |
| Was the trial ended prematurely?                     | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to investigate tailoring of recombinant follicle stimulating hormone (rFSH) treatment in subjects with chronic anovulation using 2 low dose protocols, by determining the proportion of cycles with monofollicular development.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 15 July 2013 |
| 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 | Ireland: 4         |
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Worldwide total number of subjects   | 24                 |
| EEA total number of subjects         | 24                 |

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)                      | 24 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 8 centres in Ireland and United Kingdom.

### Pre-assignment

Screening details:

A total of 24 subjects were enrolled in the study. Out of 24 only 21 subjects completed the study; 2 subjects discontinued due to hyper-response and 1 subject as per investigator's decision.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Low Dose Gonal-f |

Arm description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International unit (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, with a final increase of 25 IU, up to maximum dose of 100 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Gonal-f                                  |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

Gonal-f at a starting dose of 50 IU was administered subcutaneously up to maximum dose of 125 IU.

|  |  |
|--|--|
| Investigational medicinal product name | Human chorionic gonadotropin (hCG)       |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

Human chorionic gonadotropin (hCG) 250 microgram (mcg) was administered subcutaneously.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Standard Low Dose Gonal-f |
|------------------|---------------------------|

Arm description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 IU for Week 1, then dose was gradually increased by 12.5 IU for two weeks, up to maximum dose of 125 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Human chorionic gonadotropin (hCG)       |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

---

Dosage and administration details:

Human chorionic gonadotropin (hCG) 250 mcg was administered subcutaneously.

|  |  |
|--|--|
| Investigational medicinal product name | Gonal-f                                  |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

Gonal-f at a starting dose of 50 IU was administered subcutaneously up to maximum dose of 75 IU.

| <b>Number of subjects in period 1</b> | Low Dose Gonal-f | Standard Low Dose Gonal-f |
|---------------------------------------|------------------|---------------------------|
| Started                               | 12               | 12                        |
| Subjects received hCG treatment       | 11               | 9 <sup>[1]</sup>          |
| Completed                             | 11               | 10                        |
| Not completed                         | 1                | 2                         |
| Consent withdrawn by subject          | 1                | 2                         |

---

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone represent the subjects who received treatment and were less than the total subjects in the arm.

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Low Dose Gonal-f |
|-----------------------|------------------|

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International unit (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, with a final increase of 25 IU, up to maximum dose of 100 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Standard Low Dose Gonal-f |
|-----------------------|---------------------------|

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 IU for Week 1, then dose was gradually increased by 12.5 IU for two weeks, up to maximum dose of 125 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

| Reporting group values             | Low Dose Gonal-f | Standard Low Dose Gonal-f | Total |
|------------------------------------|------------------|---------------------------|-------|
| Number of subjects                 | 12               | 12                        | 24    |
| Age categorical<br>Units: Subjects |                  |                           |       |

|   |                |                |    |
|---|----------------|----------------|----|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 30.8<br>± 2.96 | 29.5<br>± 3.75 | -  |
| Gender, Male/Female<br>Units: Subjects                                  |                |                |    |
| Female  | 12             | 12             | 24 |
| Male  | 0              | 0              | 0  |

## End points

### End points reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Low Dose Gonal-f |
|-----------------------|------------------|

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International unit (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, with a final increase of 25 IU, up to maximum dose of 100 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Standard Low Dose Gonal-f |
|-----------------------|---------------------------|

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 IU for Week 1, then dose was gradually increased by 12.5 IU for two weeks, up to maximum dose of 125 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

### Primary: Percentage of Cycles With Monofollicular Development

|                 |   |
|-----------------|---|
| End point title | Percentage of Cycles With Monofollicular Development <sup>[1]</sup> |
|-----------------|---|

End point description:

The monofollicular development was defined as the number of cycles with monofollicular development only one Follicle greater than or equal to ( $\geq$ ) 17 millimeter (mm) and no other follicles  $\geq$  14 mm following up to 4 weeks Gonal-f treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline up to 4 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Data not assessed since study was terminated early due to delay in providing additional drug.

| End point values            | Low Dose Gonal-f | Standard Low Dose Gonal-f |  |  |
|-----------------------------|------------------|---------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[2]</sup> | 0 <sup>[3]</sup>          |  |  |
| Units: percentage of cycles |                  |                           |  |  |
| number (not applicable)     |                  |                           |  |  |

Notes:

[2] - Data not assessed since study was terminated early due to delay in providing additional drug.

[3] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Cycles With Bifollicular Development

|                 |  |
|-----------------|--|
| End point title | Percentage of Cycles With Bifollicular Development |
|-----------------|--|

End point description:

The bifollicular development was defined as the number of cycles with bifollicular development of only two follicles greater than or equal to 17 mm.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
Baseline up to 4 weeks

| End point values            | Low Dose Gonal-f | Standard Low Dose Gonal-f |  |  |
|-----------------------------|------------------|---------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[4]</sup> | 0 <sup>[5]</sup>          |  |  |
| Units: percentage of cycles |                  |                           |  |  |
| number (not applicable)     |                  |                           |  |  |

Notes:

[4] - Data not assessed since study was terminated early due to delay in providing additional drug.

[5] - Data not assessed since study was terminated early due to delay in providing additional drug.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Cycles with Multifollicular Development

|   |   |
|---|---|
| End point title   | Percentage of Cycles with Multifollicular Development |
| End point description:<br>The multifollicular development was defined as the number of cycles with multifollicular development of three or more follicles $\geq 14$ millimetre. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline up to 4 weeks  |   |

| End point values            | Low Dose Gonal-f | Standard Low Dose Gonal-f |  |  |
|-----------------------------|------------------|---------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[6]</sup> | 0 <sup>[7]</sup>          |  |  |
| Units: percentage of cycles |                  |                           |  |  |
| number (not applicable)     |                  |                           |  |  |

Notes:

[6] - Data not assessed since study was terminated early due to delay in providing additional drug.

[7] - Data not assessed since study was terminated early due to delay in providing additional drug.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of ovulatory cycles

|  |                                |
|--|--------------------------------|
| End point title  | Percentage of ovulatory cycles |
| End point description:<br>Ovulation was defined as a serum progesterone (P4 ) level $\geq 10$ nanogram per milliliter (ng/mL) or Clinical Pregnancy. Clinical pregnancy was defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It excludes ectopic pregnancy. |                                |
| End point type   | Secondary                      |

End point timeframe:

Baseline up to 42 days post human chorionic gonadotrophin (hCG) administration

| End point values            | Low Dose Gonal-f | Standard Low Dose Gonal-f |  |  |
|-----------------------------|------------------|---------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[8]</sup> | 0 <sup>[9]</sup>          |  |  |
| Units: percentage of cycles |                  |                           |  |  |
| number (not applicable)     |                  |                           |  |  |

Notes:

[8] - Data not assessed since study was terminated early due to delay in providing additional drug.

[9] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Cycles Wherein Human Chorionic Gonadotropin (hCG) was not Administered

|                 |  |
|-----------------|--|
| End point title | Percentage of Cycles Wherein Human Chorionic Gonadotropin (hCG) was not Administered |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 4 weeks

| End point values            | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type          | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[10]</sup> | 0 <sup>[11]</sup>         |  |  |
| Units: percentage of cycles |                   |                           |  |  |
| number (not applicable)     |                   |                           |  |  |

Notes:

[10] - Data not assessed since study was terminated early due to delay in providing additional drug.

[11] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Cycles Resulting in Clinical Pregnancy

|                 |  |
|-----------------|--|
| End point title | Percentage of Cycles Resulting in Clinical Pregnancy |
|-----------------|--|

End point description:

Clinical pregnancy was defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It excludes ectopic pregnancy.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|



End point timeframe:  
35-42 days post hCG administration

| End point values            | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type          | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[12]</sup> | 0 <sup>[13]</sup>         |  |  |
| Units: percentage of cycles |                   |                           |  |  |
| number (not applicable)     |                   |                           |  |  |

Notes:

[12] - Data not assessed since study was terminated early due to delay in providing additional drug.

[13] - Data not assessed since study was terminated early due to delay in providing additional drug.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Multiple Pregnancy

|  |                              |
|--|------------------------------|
| End point title  | Number of Multiple Pregnancy |
| End point description:<br>Multiple pregnancy is a pregnancy where more than one fetus develops simultaneously in the womb. There are two types of twinning—identical and fraternal. Identical twins represent the splitting of a single fertilized zygote (union of two gametes or male/female sex cells that produce a developing fetus) into two separate individuals. |                              |
| End point type   | Secondary                    |
| End point timeframe:<br>35-42 days post hCG administration   |                              |

| End point values            | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type          | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[14]</sup> | 0 <sup>[15]</sup>         |  |  |
| Units: subjects             |                   |                           |  |  |
| number (not applicable)     |                   |                           |  |  |

Notes:

[14] - Data not assessed since study was terminated early due to delay in providing additional drug.

[15] - Data not assessed since study was terminated early due to delay in providing additional drug.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Fetuses

|                        |                   |
|------------------------|-------------------|
| End point title        | Number of Fetuses |
| End point description: |                   |
| End point type         | Secondary         |

End point timeframe:  
35-42 days post hCG administration

| End point values            | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type          | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[16]</sup> | 0 <sup>[17]</sup>         |  |  |
| Units: fetuses              |                   |                           |  |  |
| number (not applicable)     |                   |                           |  |  |

Notes:

[16] - Data not assessed since study was terminated early due to delay in providing additional drug.

[17] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Miscarriages After Confirmation of Clinical Pregnancy

|                 |   |
|-----------------|---|
| End point title | Number of Miscarriages After Confirmation of Clinical Pregnancy |
|-----------------|---|

End point description:

Miscarriages were calculated per clinical pregnancy, and clinical pregnancy was defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or confirmed by clinical signs of pregnancy. It excludes ectopic pregnancy.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

35-42 days post hCG administration

| End point values            | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type          | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed | 0 <sup>[18]</sup> | 0 <sup>[19]</sup>         |  |  |
| Units: subjects             |                   |                           |  |  |
| number (not applicable)     |                   |                           |  |  |

Notes:

[18] - Data not assessed since study was terminated early due to delay in providing additional drug.

[19] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Ovarian Hyper Stimulation Syndrome (OHSS)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with Ovarian Hyper Stimulation Syndrome (OHSS) |
|-----------------|---|

End point description:

OHSS was defined as an exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations, classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, hemodynamic and metabolic

complications. Safety population included all subjects who were randomised and received at least 1 Gonal-f injection. Here "99999" signifies data was not evaluable for this outcome measure.

|                                       |           |
|---------------------------------------|-----------|
| End point type                        | Secondary |
| End point timeframe:                  |           |
| Up to 42 days post hCG administration |           |

| End point values            | Low Dose Gonal-f | Standard Low Dose Gonal-f |  |  |
|-----------------------------|------------------|---------------------------|--|--|
| Subject group type          | Reporting group  | Reporting group           |  |  |
| Number of subjects analysed | 12               | 12                        |  |  |
| Units: subjects             |                  |                           |  |  |
| number (not applicable)     | 0                | 0                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Recombinant Follicle Stimulating Hormone (rFSH) Stimulation

|                        |   |
|------------------------|---|
| End point title        | Duration of Recombinant Follicle Stimulating Hormone (rFSH) Stimulation |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline up to 4 weeks |   |

| End point values                     | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|--------------------------------------|-------------------|---------------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed          | 0 <sup>[20]</sup> | 0 <sup>[21]</sup>         |  |  |
| Units: days                          |                   |                           |  |  |
| arithmetic mean (standard deviation) | ()                | ()                        |  |  |

Notes:

[20] - Data not assessed since study was terminated early due to delay in providing additional drug.

[21] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total Dose of Recombinant Follicle Stimulating Hormone (r-FSH) Administered per Cycle

|                 |   |
|-----------------|---|
| End point title | Total Dose of Recombinant Follicle Stimulating Hormone (r-FSH) Administered per Cycle |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 4 weeks

| End point values                     | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|--------------------------------------|-------------------|---------------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed          | 0 <sup>[22]</sup> | 0 <sup>[23]</sup>         |  |  |
| Units: IU                            |                   |                           |  |  |
| arithmetic mean (standard deviation) | ()                | ()                        |  |  |

Notes:

[22] - Data not assessed since study was terminated early due to delay in providing additional drug.

[23] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Anti-Mullerian Hormone (AMH) levels at Week 4

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Anti-Mullerian Hormone (AMH) levels at Week 4 |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 4

| End point values                     | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|--------------------------------------|-------------------|---------------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed          | 0 <sup>[24]</sup> | 0 <sup>[25]</sup>         |  |  |
| Units: nanogram/milliliter (ng/mL)   |                   |                           |  |  |
| arithmetic mean (standard deviation) | ()                | ()                        |  |  |

Notes:

[24] - Data not assessed since study was terminated early due to delay in providing additional drug.

[25] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Testosterone Levels

|                 |                     |
|-----------------|---------------------|
| End point title | Testosterone Levels |
|-----------------|---------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline

| End point values                     | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|--------------------------------------|-------------------|---------------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed          | 0 <sup>[26]</sup> | 0 <sup>[27]</sup>         |  |  |
| Units: ng/mL                         |                   |                           |  |  |
| arithmetic mean (standard deviation) | ()                | ()                        |  |  |

Notes:

[26] - Data not assessed since study was terminated early due to delay in providing additional drug.

[27] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Sex Hormone Binding Globulin (SHBG) levels

|                 |  |
|-----------------|--|
| End point title | Sex Hormone Binding Globulin (SHBG) levels |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline

| End point values                     | Low Dose Gonal-f  | Standard Low Dose Gonal-f |  |  |
|--------------------------------------|-------------------|---------------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed          | 0 <sup>[28]</sup> | 0 <sup>[29]</sup>         |  |  |
| Units: ng/mL                         |                   |                           |  |  |
| arithmetic mean (standard deviation) | ()                | ()                        |  |  |

Notes:

[28] - Data not assessed since study was terminated early due to delay in providing additional drug.

[29] - Data not assessed since study was terminated early due to delay in providing additional drug.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline up to 8 months.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Standard Low Dose Gonal-f |
|-----------------------|---------------------------|

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International Units (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, up to maximum dose of 125 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Low Dose Gonal-f |
|-----------------------|------------------|

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International unit (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, with a final increase of 25 IU, up to maximum dose of 100 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

| Serious adverse events                            | Standard Low Dose Gonal-f | Low Dose Gonal-f |  |
|---|---------------------------|------------------|--|
| Total subjects affected by serious adverse events |                           |                  |  |
| subjects affected / exposed                       | 1 / 12 (8.33%)            | 0 / 12 (0.00%)   |  |
| number of deaths (all causes)                     | 0                         | 0                |  |
| number of deaths resulting from adverse events    | 0                         | 0                |  |
| Pregnancy, puerperium and perinatal conditions    |                           |                  |  |
| Abortion spontaneous                              |                           |                  |  |
| alternative assessment type: Non-systematic       |                           |                  |  |
| subjects affected / exposed                       | 1 / 12 (8.33%)            | 0 / 12 (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 %

| <b>Non-serious adverse events</b>   | Standard Low Dose<br>Gonal-f   | Low Dose Gonal-f   |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 3 / 12 (25.00%)  | 2 / 12 (16.67%)  |  |
| Nervous system disorders<br>Headache<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br><br>0  | 1 / 12 (8.33%)<br><br>1  |  |
| General disorders and administration site conditions<br>Pain<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br><br>1  | 0 / 12 (0.00%)<br><br>0  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry Mouth<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal tenderness<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br><br>1<br><br>1 / 12 (8.33%)<br><br>1<br><br>1 / 12 (8.33%)<br><br>1<br><br>0 / 12 (0.00%)<br><br>0 | 0 / 12 (0.00%)<br><br>0<br><br>0 / 12 (0.00%)<br><br>0<br><br>0 / 12 (0.00%)<br><br>0<br><br>1 / 12 (8.33%)<br><br>1 |  |
| Reproductive system and breast disorders<br>Breast tenderness<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)  | 1 / 12 (8.33%)<br><br>1  | 0 / 12 (0.00%)<br><br>0  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Vaginal discharge                           |                |                |  |
| alternative assessment type: Non-systematic |                |                |  |
| subjects affected / exposed                 | 1 / 12 (8.33%) | 0 / 12 (0.00%) |  |
| occurrences (all)                           | 1              | 0              |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 24 October 2013 | <ul style="list-style-type: none"><li>• The number of subjects planned to be enrolled in the study was updated to 116, a total of 55 subjects were planned to be enrolled in each arm.</li><li>• Inclusion Criterion was added to ensure only subjects with clinically significant abnormal serum levels of Prolactin (PRL) in the early follicular phase were excluded. This change was made to ensure subjects with abnormal but not clinically significant serum levels of PRL were able to participate in the study.</li><li>• Inclusion Criteria 8 and 9 were updated to include laparoscopy as an acceptable method to assess normal uterine cavity and tube patency in addition to hysteroscopy, Hysterosalpingography (HSG), or ultrasound scan. This change was made to ensure that all methods by which tube patency may be assessed were included.</li><li>• Amended the PP protocol population definition in order to clarify the analysis population.</li></ul> |

Notes:

### 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.

Study was terminated because of delays in sourcing replacement Investigational Medicinal Product (IMP) for the study due to manufacturing delays hence the outcome measure was not assessed.

Notes: