



Clinical trial results:

Does the DPP4 Inhibitor (Sitagliptin) Increase Endometrial Mesenchymal Stem Cells in Women with Recurrent Miscarriage?

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2016-001120-54 |
| Trial protocol | GB |
| Global end of trial date | 12 February 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 27 February 2020 |
| First version publication date | 27 February 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | SQ167015 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University Hospitals Coventry and Warwickshire NHS Trust |
| Sponsor organisation address | Clifford Bridge Road, Coventry, United Kingdom, CV2 2DX |
| Public contact | Mrs Ceri Jones, University Hospitals Coventry and Warwickshire NHS Trust, +44 2476965031, Ceri.Jones@uhcw.nhs.uk |
| Scientific contact | Professor Siobhan Quenby and Dr Shreeya Tewary, University Hospitals Coventry and Warwickshire NHS Trust, +44 2476967528, Siobhan.Quenby@uhcw.nhs.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 | 23 October 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 February 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 February 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the effect of Sitagliptin on endometrial mesenchymal stem cell count. This will be assessed by the number of colonies per thousand endometrial stromal cells after 3 months of Sitagliptin (100mg) vs. 3 months of placebo, determined by a clonogenic assay.

The pre-specified primary outcome measure was the CFU count per 1000EnSC seeded after 3 cycles of sitagliptin or placebo. However, to mitigate against potential loss of data in case of infection, a total of 1500cells were seeded in 3 wells of a 6-well plate per sample. As there were no obvious criteria to exclude the colony count from a given well, the results are presented as CFU count per 1500EnSC.

Protection of trial subjects:

Patients were reviewed every 4 weeks to assess for any side effects, with an independent advisor overseeing the trial who was very familiar with using sitagliptin. The endometrial biopsies were taken using a simple manual suction device commonly used in gynaecology clinics. The sampler is inserted through the cervix into the uterus to take the endometrial biopsy. The patients were warned beforehand that the sampler can cause some pelvic pain and cramps due to uterine contractions. They were advised that 400mg of Ibuprofen and 1g of Paracetamol can be taken prior to their visit and Entonox is available to use when the biopsy is being taken. They were also told to bring a sanitary pad as they may experience some spotting after the procedure. It was explained to patients that they must not try for a pregnancy while in the trial, as agreed on the consent form. They were asked to do a pregnancy test at home every 2 weeks, each time a patient attended for a face-face consultation, and before each endometrial biopsy. In the event of a positive pregnancy test patients were asked to stop the medication immediately.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 14 September 2016 |
| 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: 38 |
| Worldwide total number of subjects | 38 |
| EEA total number of subjects | 38 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| 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) | 38 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The date of enrolment of the first participant was 15th September 2016.

Single centre: University Hospitals Coventry and Warwickshire (UHCW) National Health Service (NHS) Trust.

Pre-assignment

Screening details:

Screened 73, Excluded (n=35)

Not meeting inclusion criteria (n=7)

Declined to participate (n=24)

Other reasons (n= 4)

Pre-assignment period milestones

| | |
|----------------------------|----|
| Number of subjects started | 38 |
|----------------------------|----|

| | |
|------------------------------|----|
| Number of subjects completed | 33 |
|------------------------------|----|

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 1 |
|----------------------------|---------------------------------|

| | |
|----------------------------|-----------------------|
| Reason: Number of subjects | Physician decision: 1 |
|----------------------------|-----------------------|

| | |
|----------------------------|--------------|
| Reason: Number of subjects | Pregnancy: 2 |
|----------------------------|--------------|

| | |
|----------------------------|----------------------|
| Reason: Number of subjects | Loss to follow up: 1 |
|----------------------------|----------------------|

Period 1

| | |
|----------------|--|
| Period 1 title | Completed overall trial (overall period) |
|----------------|--|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

| | |
|---------------|--------------|
| Blinding used | Double blind |
|---------------|--------------|

| | |
|---------------|---|
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |
|---------------|---|

Blinding implementation details:

Participants, investigators, research midwives and nurses remained blinded to the IMP allocation throughout the duration of the trial. The IMP was supplied as blinded packs of Sitagliptin/placebo 100mg capsules.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-------------|
| Arm title | Sitagliptin |
|------------------|-------------|

Arm description: -

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-------------|
| Investigational medicinal product name | Sitagliptin |
|--|-------------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|--------|
| Pharmaceutical forms | Tablet |
|----------------------|--------|

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Encapsulated tablet containing 100mg of active Sitagliptin.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description: -

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Encapsulated tablet containing 100mg of placebo

| Number of subjects in period 1^[1] | Sitagliptin | Placebo |
|---|-------------|---------|
| Started | 16 | 17 |
| Completed | 16 | 17 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics have been reported for those that have completed the trial (n=33).

Baseline characteristics

Reporting groups

| | |
|--------------------------------|-------------|
| Reporting group title | Sitagliptin |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | Sitagliptin | Placebo | Total |
|--|-------------|---------|-------|
| Number of subjects | 16 | 17 | 33 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 34.5 | 31.3 | |
| standard deviation | ± 4.20 | ± 3.69 | - |
| Gender categorical Units: Subjects | | | |
| Female | 16 | 17 | 33 |
| Male | 0 | 0 | 0 |
| BMI Units: kg/m2 | | | |
| arithmetic mean | 26.9 | 26.3 | |
| standard deviation | ± 4.67 | ± 4.59 | - |
| Number of previous miscarriages Units: miscarriages | | | |
| arithmetic mean | 6.6 | 7.6 | |
| standard deviation | ± 3.2 | ± 3.5 | - |

End points

End points reporting groups

| | |
|--------------------------------|-------------|
| Reporting group title | Sitagliptin |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

Primary: The number of colonies per 1500 endometrial stromal cells after 3 months of Sitagliptin (100mg) vs. 3 months of placebo, determined by a clonogenic assay

| | |
|------------------------|---|
| End point title | The number of colonies per 1500 endometrial stromal cells after 3 months of Sitagliptin (100mg) vs. 3 months of placebo, determined by a clonogenic assay |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and 3 months | |

| End point values | Sitagliptin | Placebo | | |
|--|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 ^[1] | 17 ^[2] | | |
| Units: per 1500 endometrial stromal cells | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline eMSC count per 1500 cells seeded | 16.1 (± 19.6) | 24.2 (± 25.6) | | |
| Final visit eMSC count per 1500 cells seeded | 27.7 (± 35.8) | 25.1 (± 27.3) | | |

Notes:

[1] - Observation for one woman missing for Final visit eMSC count per 1500 cells seeded.

[2] - Observation for one woman missing for Baseline eMSC count per 1500 cells seeded.

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Primary analysis |
| Comparison groups | Sitagliptin v Placebo |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.15 |
| Method | Poisson regression model |
| Parameter estimate | Rate ratio |
| Point estimate | 1.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.26 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

14/09/2016 - 12/02/2018

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Sitagliptin |
|-----------------------|-------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Sitagliptin | Placebo | |
|---|--|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | Additional description: Hospitalisation - Participant was admitted to A&E with abdominal pain. Pregnancy test performed whilst at hospital was positive. Participant was discharged from A&E the same day. | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 | Sitagliptin | Placebo | |
|---|-----------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 12 / 19 (63.16%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 7 / 19 (36.84%) | |
| occurrences (all) | 2 | 7 | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 19 (0.00%) | |
| occurrences (all) | 2 | 0 | |

| | | | |
|--|---------------------|---------------------|--|
| Migraine subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 19 (0.00%) 0 | |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| General disorders and administration site conditions | | | |
| Chills subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 19 (0.00%) 0 | |
| Pain subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 19 (0.00%) 0 | |
| Thirst subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 19 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Eye disorders | | | |
| Extraocular muscle paresis subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 19 (5.26%) 1 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 19 (0.00%) 0 | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Dry mouth | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dry throat | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Night sweats | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Androgenetic alopecia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |

| | | | |
|---|--|--|--|
| Nervousness subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0 | 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 18 November 2016 | A temporary halt of the trial, after 4 patients had been randomised. As some patient's had their blood tests repeated and recruited using the second eligible test results. Allow time to prepare the protocol amendment with clearer guidance to recruitment and eligibility criteria. |
| 06 December 2016 | Amendment to request the restart of the trial following temporary halt. Amendment to the trial protocol, participant flow in line with current practice, eligibility criteria regarding renal and hepatic function. Patients identified from the implantation clinic will be referred to the recurrent miscarriage clinic to have routine blood tests to ensure there is no cause for their miscarriages before being recruited to SIMPLANT. Consent will be taken at a time that suits the patient after they have had sufficient time to read the patient information leaflet and eligibility has been confirmed. Pharmacovigilance and Safety monitoring has been edited to reflect correct reporting procedures to the Sponsor and regulatory authorities. Unblinding procedure update, as originally, Sharpe Clinical Services were going to make the master unblinding list and provide the code break envelopes however this was done by an independent statistician. |
| 02 May 2017 | Amendment to the protocol to allow randomisation of up to 40 participants, rather than 34 participants as previously planned, and an extension of the recruitment period. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--------------------------------|------------------|
| 18 November 2016 | A temporary halt of the trial. | 06 December 2016 |

Notes:

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31928963>