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	Pregnancy: 2
Reason: Number of subjects	Physician decision: 1
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 be 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	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Thirst			
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Eye disorders			
Extraocular muscle paresis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Abdominal discomfort			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	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	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	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. Pharmacovigilence 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