Clinical trial results:
A Double-Blind, Double-Dummy, Randomized, Two-arm, Multicenter Study Comparing the Efficacy, Safety, and Tolerability of Oral Dydrogesterone 30 mg Daily Versus Intravaginal Micronized Progesterone Capsules 600 mg Daily for Luteal Support in In-Vitro Fertilization (LOTUS I)

Summary

EudraCT number	2012-002215-26
Trial protocol	BE AT ES FI
Global end of trial date	23 March 2016

Results information

Result version number	v1 (current)
This version publication date	18 July 2019
First version publication date	18 July 2019

Trial information

Trial identification

Sponsor protocol code	M13-563

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01850030
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbott Laboratories GmbH
Sponsor organisation address	Freundallee 9A, Hannover, Germany, 30173
Public contact	Senior Global Medical Director, Abbott Laboratories GmbH, claire.pexman-fieth@abbott.com
Scientific contact	Senior Global Medical Director, Abbott Laboratories GmbH, claire.pexman-fieth@abbott.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	23 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of oral dydrogesterone 10 milligrams (mg) three times daily (TID) versus micronized progesterone vaginal capsules 200 mg TID. The primary efficacy variable was the presence of fetal heartbeats at 12 weeks gestation determined by transvaginal ultrasound.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice and the applicable national regulations to assure that the rights, safety, and well-being of the participating study subjects were protected, consistent with the ethical principles that have their origin in the Declaration of Helsinki. All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 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	Austria: 15
Country: Number of subjects enrolled	Belgium: 390
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Germany: 136
Country: Number of subjects enrolled	Israel: 144
Country: Number of subjects enrolled	Russian Federation: 216
Country: Number of subjects enrolled	Spain: 120
Worldwide total number of subjects	1031
EEA total number of subjects	671

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1031
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult female subjects aged >18 and <42 years entered this randomized, double-blind, double-dummy multicenter study from August 2013. The study was conducted at 38 sites in Europe, Russia and Israel. The study completed in March 2016.

Pre-assignment

Screening details:

Subjects were premenopausal and had a documented history of infertility, with a clinically indicated protocol for induction of in vitro fertilization with a fresh embryo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Oral Dydrogesterone

Arm description:

Subjects were randomized to receive oral dydrogesterone 10 mg tablets TID (30 mg daily) and placebo intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) from Visit 2 (Day 1).
At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta human chorionic gonadotropin (beta-hCG) or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

Arm type	Experimental
Investigational medicinal product name	Placebo intravaginal micronized progesterone capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal capsule
Routes of administration	Vaginal use

Dosage and administration details:

Subjects received placebo intravaginal micronized progesterone 200 mg capsules TID from Day 1 to Week 10 (if pregnancy confirmed at Visit 4).

Investigational medicinal product name	Dydrogesterone
Investigational medicinal product code	
Other name	Duphaston
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received oral dydrogesterone 10 mg tablets TID from Day 1 to Week 10 (if pregnancy confirmed at Visit 4).

Arm title	Intravaginal Micronized Progesterone

Arm description:

Subjects were randomized to receive intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) and placebo oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1).
At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

Arm type	Active comparator

Investigational medicinal product name	Placebo dydrogesterone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo dydrogesterone 10 mg tablets TID from Day 1 to Week 10 (if pregnancy confirmed at Visit 4).

Investigational medicinal product name	Intravaginal micronized progesterone capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal capsule
Routes of administration	Vaginal use

Dosage and administration details:

Subjects received intravaginal micronized progesterone 200 mg capsules TID from Day 1 to Week 10 (if pregnancy confirmed at Visit 4).

Number of subjects in period 1	Oral Dydrogesterone	Intravaginal Micronized Progesterone
Started	520	511
Confirmed pregnancy at Day 15	234	217
Ongoing pregnancy at Week 6	197	169
Confirmed pregnancy at Week 10	187	158
Giving live birth(s)	172 [1]	142
Completed	173	142
Not completed	347	369
Pregnancy not confirmed at Day 15	248	249
Consent withdrawn by subject	3	4
Adverse event, non-fatal	64	82
Lost to follow-up	5	5
Lack of efficacy	3	1
Protocol deviation	24	28

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: One subject was recorded as lost to follow-up and was recorded as having a live birth.

Baseline characteristics

Reporting groups	
Reporting group title	Oral Dydrogesterone
Reporting group description:	
Subjects were randomized to receive oral dydrogesterone 10 mg tablets TID (30 mg daily) and placebo intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) from Visit 2 (Day 1). At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta human chorionic gonadotropin (beta-hCG) or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).	
Reporting group title	Intravaginal Micronized Progesterone
Reporting group description:	
Subjects were randomized to receive intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) and placebo oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1). At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).	

Reporting group values	Oral Dydrogesterone	Intravaginal Micronized Progesterone	Total
Number of subjects	520	511	1031
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)	520	511	1031
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	520	511	1031
Male	0	0	0

End points

End points reporting groups

Reporting group title	Oral Dydrogesterone

Reporting group description:

Subjects were randomized to receive oral dydrogesterone 10 mg tablets TID (30 mg daily) and placebo intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) from Visit 2 (Day 1).
At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta human chorionic gonadotropin (beta-hCG) or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

Reporting group title	Intravaginal Micronized Progesterone

Reporting group description:

Subjects were randomized to receive intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) and placebo oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1).
At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

Primary: Pregnancy Rate at Visit 6 (Week 10): Per Protocol (PP) Subject Sample

End point title	Pregnancy Rate at Visit 6 (Week 10): Per Protocol (PP) Subject Sample

End point description:

The pregnancy rate, defined as the percentage of subjects for whom a fetal heartbeat was detected by transvaginal ultrasound at Visit 6 (Week 10) (12 weeks gestation), in the PP Subject Sample is presented. The PP Subject Sample consisted of all subjects who were allocated to treatment who received at least one administration of study drug, had a successful single or dual embryo transfer at Visit 3 (Day 3 to 6) and did not have any major protocol deviations unrelated to treatment. Subjects who prematurely discontinued after having a pregnancy test were counted as failures if the test was negative or if the test was positive but the reason for discontinuation was related to study drug or pregnancy related issues.

End point type	Primary

End point timeframe:

At Visit 6 (Week 10).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	492	475		
Units: Percentage of subjects				
number (confidence interval 95%)	37.6 (33.3 to 42.1)	33.1 (28.8 to 37.5)		

Statistical analyses

Statistical analysis title	Treatment difference: PP Subject Sample
Comparison groups	Oral Dydrogesterone v Intravaginal Micronized Progesterone

Number of subjects included in analysis	967
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	10.6

Notes:

[1] - To show that oral dydrogesterone was non-inferior to intravaginal micronized progesterone, a two-sided 95% confidence interval (CI) with a non-inferiority margin of 10% for the difference in pregnancy rates was used.

Primary: Pregnancy Rate at Visit 6 (Week 10): Full Analysis (FA) Subject Sample

End point title	Pregnancy Rate at Visit 6 (Week 10): Full Analysis (FA) Subject Sample

End point description:

The pregnancy rate, defined as the percentage of subjects for whom a fetal heartbeat was detected by transvaginal ultrasound at Visit 6 (Week 10) (12 weeks gestation), in the FA Subject Sample is presented. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues. Subjects who prematurely discontinued after having a pregnancy test were counted as failures if the test was negative or if the test was positive but the reason for discontinuation was related to study drug or pregnancy related issues.

End point type	Primary

End point timeframe:

At Visit 6 (Week 10).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	477		
Units: Percentage of subjects				
number (confidence interval 95%)	37.6 (33.4 to 42.1)	33.1 (28.9 to 37.6)		

Statistical analyses

Statistical analysis title	Treatment difference: FA Subject Sample
Comparison groups	Oral Dydrogesterone v Intravaginal Micronized Progesterone

Number of subjects included in analysis	974
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference (%)
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	10.6

Notes:

[2] - To show that oral dydrogesterone was non-inferior to intravaginal micronized progesterone, a two-sided 95% CI with a non-inferiority margin of 10% for the difference in pregnancy rates was used.

Secondary: Pregnancy Rate at Visit 4 (Day 15)

End point title	Pregnancy Rate at Visit 4 (Day 15)

End point description:

The percentage of subjects who were pregnant at Visit 4 (Day 15) as determined by a positive beta-hCG serum test are presented for the FA Subject Sample. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

End point type	Secondary

End point timeframe:

At Visit 4 (Day 15).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	477		
Units: Percentage of subjects				
number (confidence interval 95%)	47.1 (42.6 to 51.6)	45.5 (41.0 to 50.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pregnancy Rate at Visit 5 (Week 6)

End point title	Pregnancy Rate at Visit 5 (Week 6)

End point description:

Ongoing pregnancy at Visit 5 (Week 6) was confirmed based on clinical evidence. The percentage of subjects in the FA Subject Sample who had pregnancy confirmed at Visit 5 are presented. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

End point type	Secondary

End point timeframe:

At Visit 5 (Week 6).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	477		
Units: Percentage of subjects				
number (confidence interval 95%)	39.6 (35.3 to 44.1)	35.4 (31.1 to 39.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abortion Rate

End point title	Abortion Rate

End point description:

The percentage of subjects in the FA Subject Sample who had an abortion (abortion rate) is presented. Subjects with abortions reported from Visit 5 (Week 6) onwards were included, since abortions reported before Visit 5 (Week 6) were considered biochemical pregnancies and were therefore not to be considered in the efficacy analysis of abortion rate. The Investigator determined whether the subject had an abortion. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

End point type	Secondary

End point timeframe:

From Visit 5 (Week 6) up to 20-24 weeks gestation (18-22 weeks pregnancy).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	477		
Units: Percentage of subjects				
number (confidence interval 95%)	1.6 (0.7 to 3.2)	2.1 (1.0 to 3.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Preterm Birth Rate

End point title	Preterm Birth Rate

End point description:

The percentage of subjects in the FA Subject Sample who had a preterm birth (preterm birth rate) is presented. The Investigator determined whether the subject had a preterm birth. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

End point type	Secondary

End point timeframe:

Up to 37 weeks of gestation (35 weeks of pregnancy).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	477		
Units: Percentage of subjects				
number (confidence interval 95%)	7.9 (5.6 to 10.6)	5.2 (3.4 to 7.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Live Birth Rate

End point title	Live Birth Rate

End point description:

The percentage of subjects in the FA Subject Sample who had at least one live birth (live birth rate) are presented. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug, had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

End point type	Secondary

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	477		
Units: Percentage of subjects				
number (confidence interval 95%)	34.6 (30.4 to 39.0)	29.8 (25.7 to 34.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthy Newborn Rate

End point title	Healthy Newborn Rate

End point description:

The percentage of subjects in the FA Subject Sample who gave birth to at least one healthy newborn (healthy newborn rate) is presented. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

End point type	Secondary

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	477		
Units: Percentage of subjects				
number (confidence interval 95%)	32.0 (27.9 to 36.3)	27.7 (23.7 to 31.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Gender of the Newborn

End point title	Gender of the Newborn

End point description:

The number of male and female live newborns is presented for the FA Subject Sample.

End point type	Other pre-specified

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer).

End point values	Oral Dydrogesterone	Intravaginal Micronized Progesterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	477		
Units: Newborns				
Male	120	88		
Female	93	70		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the start of treatment (Day 1) to the follow-up phone call at Visit 10 (30 days after delivery).

Adverse event reporting additional description:

The Safety Subject Sample consists of all subjects who were allocated to treatment and received at least one administration of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Oral Dydrogesterone

Reporting group description:

Subjects were randomized to receive oral dydrogesterone 20 mg tablets TID (30 mg daily) and placebo intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) from Visit 2 (Day 1).
At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

Reporting group title	Intravaginal Micronized Progesterone

Reporting group description:

Subjects were randomized to receive intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) and placebo oral dydrogesterone 20 mg tablets TID (30 mg daily) from Visit 2 (Day 1).
At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

Serious adverse events	Oral Dydrogesterone	Intravaginal Micronized Progesterone	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 518 (10.81%)	68 / 511 (13.31%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypertension			
subjects affected / exposed	1 / 518 (0.19%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	2 / 518 (0.39%)	3 / 511 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Selective abortion			
subjects affected / exposed	1 / 518 (0.19%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labour induction			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	9 / 518 (1.74%)	15 / 511 (2.94%)	
occurrences causally related to treatment / all	0 / 9	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion threatened			
subjects affected / exposed	2 / 518 (0.39%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion missed			
subjects affected / exposed	6 / 518 (1.16%)	9 / 511 (1.76%)	
occurrences causally related to treatment / all	0 / 6	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abortion			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion complete			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion of ectopic pregnancy			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	4 / 518 (0.77%)	4 / 511 (0.78%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical incompetence			
subjects affected / exposed	3 / 518 (0.58%)	3 / 511 (0.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperemesis gravidarum			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature labour			
subjects affected / exposed	4 / 518 (0.77%)	2 / 511 (0.39%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature rupture of membranes			
subjects affected / exposed	1 / 518 (0.19%)	2 / 511 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature delivery			

subjects affected / exposed	1 / 518 (0.19%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Threatened labour			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal death			
subjects affected / exposed	0 / 518 (0.00%)	6 / 511 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal distress syndrome			
subjects affected / exposed	1 / 518 (0.19%)	2 / 511 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal disorder			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal hypokinesia			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			
subjects affected / exposed	2 / 518 (0.39%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HELLP syndrome			
subjects affected / exposed	0 / 518 (0.00%)	2 / 511 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oligohydramnios			

subjects affected / exposed	2 / 518 (0.39%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyhydramnios			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature baby			
subjects affected / exposed	2 / 518 (0.39%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature separation of placenta			
subjects affected / exposed	1 / 518 (0.19%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage in pregnancy			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroplacental haematoma			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy of unknown location			
subjects affected / exposed	1 / 518 (0.19%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine contractions during pregnancy			
subjects affected / exposed	1 / 518 (0.19%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical cord around neck			

subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical cord vascular disorder			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blighted ovum			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal growth restriction			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retained placenta or membranes			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum haemorrhage			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	8 / 518 (1.54%)	5 / 511 (0.98%)	
occurrences causally related to treatment / all	1 / 8	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adnexal torsion			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian haemorrhage			

subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortened cervix			
subjects affected / exposed	1 / 518 (0.19%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 518 (0.19%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Foetal heart rate abnormal			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

C-reactive protein increased			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder injury			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Trisomy 21			
subjects affected / exposed	1 / 518 (0.19%)	2 / 511 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trisomy 13			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery atresia			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Univentricular heart			

subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital tricuspid valve atresia			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spina bifida			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital hydrocephalus			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Turner's Syndrome			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Foetal heart rate deceleration			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal heart rate disorder			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Orthostatic intolerance			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 518 (0.19%)	3 / 511 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			

subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 518 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 518 (0.19%)	0 / 511 (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: 5 %

Non-serious adverse events	Oral Dydrogesterone	Intravaginal Micronized Progesterone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 518 (30.12%)	147 / 511 (28.77%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	39 / 518 (7.53%)	40 / 511 (7.83%)	
occurrences (all)	40	41	
Pregnancy, puerperium and perinatal conditions			
Pregnancy of unknown location			

subjects affected / exposed	19 / 518 (3.67%)	29 / 511 (5.68%)	
occurrences (all)	19	29	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 518 (5.21%)	32 / 511 (6.26%)	
occurrences (all)	31	36	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	60 / 518 (11.58%)	46 / 511 (9.00%)	
occurrences (all)	74	54	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	24 / 518 (4.63%)	31 / 511 (6.07%)	
occurrences (all)	25	33	
Nausea			
subjects affected / exposed	44 / 518 (8.49%)	26 / 511 (5.09%)	
occurrences (all)	46	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2013	Implemented a change in the time for embryo transfer at Visit 3 from 'Day2/3' to 'Day 2 to Day 5'.
24 November 2015	The definition and AE/serious AE reporting requirements of a biochemical pregnancy and clinical pregnancy were clarified. Clarified that pregnancy was to be confirmed according to clinical evidence. The definition of miscarriage and explanatory text on the expectedness of early miscarriages before Week 10 of pregnancy (12 weeks gestation) were also added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported