Clinical trial results:
Effectiveness of progesterone to prevent miscarriage in women with early pregnancy bleeding: A randomised placebo-controlled trial (PRISM Trial: PRogesterone In Spontaneous Miscarriage Trial)

Summary

EudraCT number	2014-002348-42
Trial protocol	GB
Global end of trial date	15 June 2018

Results information

Result version number	v1 (current)
This version publication date	25 May 2019
First version publication date	25 May 2019

Trial information

Trial identification

Sponsor protocol code	RG_13-151

Additional study identifiers

ISRCTN number	ISRCTN14163439
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Room 119, Aston Webb Building, Edgbaston, Birmingham, United Kingdom, B15 2TT
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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	26 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2018
Global end of trial reached?	Yes
Global end of trial date	15 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that in women presenting with vaginal bleeding in the first trimester, progesterone (vaginal capsules 400mg twice daily), started as soon as possible after a scan has demonstrated a visible intrauterine gestation sac and continued to 16 completed weeks of gestation, compared with placebo, increases maternities with live births beyond 34 completed weeks by at least 5%.

Protection of trial subjects:

No special measures were required to minimise pain or distress in this patient population.

Background therapy:

Progesterone, produced by the corpus luteum in the ovary, is necessary to prepare the endometrium for implantation of the embryo, and thus is an essential hormone for a successful pregnancy. More progesterone is produced when an embryo implants in the endometrium and during early placental development. Subsequently, from about 12 weeks of pregnancy, the placenta becomes the dominant source of progesterone. The physiologic importance of progesterone has prompted researchers, physicians and patients to consider progesterone supplementation during early pregnancy to prevent miscarriages. The multicentre, randomised, parallel-group, double-blind, placebo-controlled PRISM (Progesterone in Spontaneous Miscarriage) Trial was designed and conducted to investigate whether treatment with progesterone would increase the live birth rate among women with early pregnancy bleeding.

Evidence for comparator:

Participants were randomly assigned in a 1:1 ratio to self-administer vaginal suppositories containing either 400mg of micronized progesterone (Utrogestan, Besins Healthcare) twice daily or matched placebo from the time of randomisation through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).

Actual start date of recruitment	19 May 2015
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: 4153
Worldwide total number of subjects	4153
EEA total number of subjects	4153

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)	18
Adults (18-64 years)	4135
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 12,862 women were identified as eligible for the PRISM trial from May 19, 2015, through to July 27, 2017 at 48 hospitals within the United Kingdom. 4153 of these women were randomly assigned to receive either progesterone (2079 women) or placebo (2074 women). The follow-up rate for the primary outcome was 97% (4038 of 4153 women).

Pre-assignment

Screening details:

Women were screened to ensure that they were eligible for the trial. Women were eligible for enrollment in the study if they were 16 to 39 years of age, pregnant, presented with vaginal bleeding, and had an intrauterine gestation sac that was visible on ultrasound, with a gestational age less than 12 completed weeks of pregnancy.

Period 1

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

Blinding implementation details:

Randomised, parallel-group, double-blind, placebo-controlled trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Progesterone

Arm description:

400mg of micronized progesterone (Utrogestan, Besins Healthcare) twice daily through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).

Arm type	Experimental
Investigational medicinal product name	Progesterone
Investigational medicinal product code	
Other name	Utrogestan
Pharmaceutical forms	Suppository
Routes of administration	Vaginal use

Dosage and administration details:

400mg twice daily from the time of randomization through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).

Arm title	Placebo

Arm description:

Matched placebo, taken twice daily from the time of randomization through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Vaginal use

Dosage and administration details:

400mg twice daily from the time of randomization through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).

Number of subjects in period 1	Progesterone	Placebo
Started	2079	2074
Completed	2025	2013
Not completed	54	61
Lost to follow-up	54	61

Baseline characteristics

Reporting groups	
Reporting group title	Progesterone
Reporting group description:	
400mg of micronized progesterone (Utrogestan, Besins Healthcare) twice daily through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).	
Reporting group title	Placebo
Reporting group description:	
Matched placebo, taken twice daily from the time of randomization through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).	

Reporting group values	Progesterone	Placebo	Total
Number of subjects	2079	2074	4153
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)	8	10	18
Adults (18-64 years)	2071	2064	4135
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	30.6	30.5	
standard deviation	± 5.1	± 5.1	-
Gender categorical Units: Subjects			
Female	2079	2074	4153
Ethnic group Units: Subjects			
White	1714	1742	3456
Black	84	79	163
South Asian	114	102	216
Other	167	151	318
Pregnancy history Units: Subjects			
Nulliparous	474	514	988
Previous preterm births (≥24 weeks, <34 weeks)	83	90	173
Neither nulliparous or previous preterm birth	1522	1470	2992
Previous miscarriage Units: Subjects			
Zero	1145	1157	2302
One or two	792	758	1550

Three or more	142	159	301
Amount of bleeding (PBAC score) Units: Subjects			
≤2	1913	1907	3820
≥3	166	167	333
Pregnancy related information Units: Subjects			
Natural conception	2030	2036	4066
Fertility Treatment	49	38	87
Estimated gestational age in days at presentation Units: Subjects			
<42	372	374	746
≥42	1707	1700	3407
Number of gestational sacs observed Units: Subjects			
One	2025	2036	4061
Two	53	38	91
Three or more	1	0	1
Fetal heart activity at presentation Units: Subjects			
Yes	1710	1701	3411
No	369	373	742

End points

End points reporting groups

Reporting group title	Progesterone
Reporting group description:	
400mg of micronized progesterone (Utrogestan, Besins Healthcare) twice daily through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).	
Reporting group title	Placebo
Reporting group description:	
Matched placebo, taken twice daily from the time of randomization through to 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks).	

Primary: Live birth ≥34 weeks

End point title	Live birth ≥34 weeks
End point description:	
End point type	Primary
End point timeframe:	
From randomisation to pregnancy end	

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2025	2013		
Units: participants	1513	1459		

Statistical analyses

Statistical analysis title	Poisson regression model
Comparison groups	Progesterone v Placebo
Number of subjects included in analysis	4038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.07
Variability estimate	Standard deviation

Secondary: Ongoing pregnancy at 12 weeks

End point title	Ongoing pregnancy at 12 weeks

End point description:

End point type	Secondary

End point timeframe:

From randomisation to 12 weeks of gestation or pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2025	2013		
Units: participants	1672	1602		

Statistical analyses

No statistical analyses for this end point

Secondary: Miscarriage <24 weeks

End point title	Miscarriage <24 weeks

End point description:

End point type	Secondary

End point timeframe:

From randomisation to pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2025	2013		
Units: participants	410	451		

Statistical analyses

No statistical analyses for this end point

Secondary: Live birth <34 weeks

End point title	Live birth <34 weeks

End point description:

End point type	Secondary

End point timeframe:

From randomisation to pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2025	2013		
Units: participants	68	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Ectopic pregnancy

End point title	Ectopic pregnancy

End point description:

End point type	Secondary

End point timeframe:

From randomisation to pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2025	2013		
Units: participants	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Stillbirth (intrauterine death ≥24 weeks)

End point title	Stillbirth (intrauterine death ≥24 weeks)

End point description:

End point type	Secondary

End point timeframe:

From randomisation to pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2025	2013		
Units: participants	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Termination

End point title	Termination

End point description:

End point type	Secondary

End point timeframe:

From randomisation to pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2025	2013		
Units: participants	34	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Gestational age in weeks at delivery

End point title	Gestational age in weeks at delivery

End point description:

End point type	Secondary

End point timeframe:

From randomisation to pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1581	1521		
Units: Days				
arithmetic mean (standard deviation)	270 (± 18)	270 (± 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Birth weight

End point title	Birth weight

End point description:

End point type	Secondary

End point timeframe:

From randomisation to pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1604	1539		
Units: Grams				
arithmetic mean (standard deviation)	3242 (± 656)	3261 (± 659)		

Statistical analyses

No statistical analyses for this end point

Secondary: Death at 28 days of neonatal life

End point title	Death at 28 days of neonatal life

End point description:

End point type	Secondary

End point timeframe:

From randomisation to pregnancy end

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1605	1533		
Units: Babies	8	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomisation to 28 days post pregnancy end	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14

Reporting groups	
Reporting group title	Progesterone
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Progesterone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	133 / 2025 (6.57%)	126 / 2013 (6.26%)	
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 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haemorrhage			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (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			
Neonatal weight loss			
subjects affected / exposed	3 / 2025 (0.15%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal jaundice			

subjects affected / exposed	4 / 2025 (0.20%)	3 / 2013 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	6 / 2025 (0.30%)	4 / 2013 (0.20%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal tightenings			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anhydramnios			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antepartum haemorrhage			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational diabetes			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational thrombocytopenia			

subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperemesis gravidarium			
subjects affected / exposed	5 / 2025 (0.25%)	6 / 2013 (0.30%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intrauterine adhesions			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal death			
subjects affected / exposed	8 / 2025 (0.40%)	2 / 2013 (0.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 8	0 / 2	
Neonatal hypoglycaemia			
subjects affected / exposed	2 / 2025 (0.10%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal infection			
subjects affected / exposed	2 / 2025 (0.10%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal poor condition			

subjects affected / exposed	0 / 2025 (0.00%)	2 / 2013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-partum haemorrhage			
subjects affected / exposed	14 / 2025 (0.69%)	16 / 2013 (0.79%)	
occurrences causally related to treatment / all	0 / 14	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			
subjects affected / exposed	0 / 2025 (0.00%)	2 / 2013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-term birth			
subjects affected / exposed	3 / 2025 (0.15%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Preterm premature rupture of membranes			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced fetal movements			
subjects affected / exposed	0 / 2025 (0.00%)	2 / 2013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured membranes			
subjects affected / exposed	4 / 2025 (0.20%)	7 / 2013 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stillbirth			
subjects affected / exposed	0 / 2025 (0.00%)	4 / 2013 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Termination of pregnancy			

subjects affected / exposed	2 / 2025 (0.10%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical flare			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Talipes calcanedualgus			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prematurity			
subjects affected / exposed	1 / 2025 (0.05%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hospitalisation			
subjects affected / exposed	0 / 2025 (0.00%)	2 / 2013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disequilibrium			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fainting			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy-related admission			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolonged hospitalisation			

subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right-sided weakness			
subjects affected / exposed	0 / 2025 (0.00%)	2 / 2013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Per vaginal bleeding			
subjects affected / exposed	13 / 2025 (0.64%)	8 / 2013 (0.40%)	
occurrences causally related to treatment / all	0 / 13	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical pathology			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
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			
Chest pain			
subjects affected / exposed	4 / 2025 (0.20%)	5 / 2013 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest infection			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortness of breath			
subjects affected / exposed	2 / 2025 (0.10%)	2 / 2013 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neonatal apnoea			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal respiratory disease			
subjects affected / exposed	2 / 2025 (0.10%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 2025 (0.05%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Acrania			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac abnormailty			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital fetal abnormality			
subjects affected / exposed	0 / 2025 (0.00%)	2 / 2013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystic fibrosis			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Down's syndrome			
subjects affected / exposed	1 / 2025 (0.05%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypospadias			
subjects affected / exposed	3 / 2025 (0.15%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal abnormality			
subjects affected / exposed	13 / 2025 (0.64%)	7 / 2013 (0.35%)	
occurrences causally related to treatment / all	0 / 13	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal tongue tie			
subjects affected / exposed	1 / 2025 (0.05%)	3 / 2013 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal vaginal skin tag			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restrictive dermopathy			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synactyly of toes			
subjects affected / exposed	1 / 2025 (0.05%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tetralogy of Fallot			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transposition of great arteries			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trisomy 21			

subjects affected / exposed	2 / 2025 (0.10%)	4 / 2013 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal neonatal cardiotocography			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal cardiomyopathy			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 2025 (0.05%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal seizures			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Visual disturbances			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforated bowel			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Haematoma			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous lump under nipple			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder lesion			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal hydronephrosis			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal kidney abnormality			

subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal megacystis bladder			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonate missing left kidney			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 2025 (0.10%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Enlarged submandibular gland			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallstones			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 2025 (0.05%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Fracture			
subjects affected / exposed	2 / 2025 (0.10%)	0 / 2013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection			
subjects affected / exposed	1 / 2025 (0.05%)	3 / 2013 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter infection			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 2025 (0.20%)	6 / 2013 (0.30%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Abnormal liver function			
subjects affected / exposed	0 / 2025 (0.00%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal poor feeding			
subjects affected / exposed	1 / 2025 (0.05%)	1 / 2013 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Progesterone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	130 / 2025 (6.42%)	141 / 2013 (7.00%)	
Pregnancy, puerperium and perinatal conditions			

Obstetric complication subjects affected / exposed occurrences (all)	130 / 2025 (6.42%) 219	141 / 2013 (7.00%) 202	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2016	The following changes were made to the protocol: 1. Clarification in the trial inclusion criteria that the early pregnancy vaginal bleeding is within the previous four days. This criterion had that have been enforced since the start of the trial, although it wasn't formally clarified in the inclusion criteria. 2. Provision of more detailed definitions for the secondary outcome measures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported