Clinical trial results:
First trimester progesterone therapy in women with a history of unexplained recurrent miscarriages: A randomised, double-blind, placebo-controlled, multi-centre trial [The PROMISE (PROgesterone in recurrent MIScarriagE) Trial] Funded by NIHR-HTA(UK) 08/38/01 for £1.2 million

Summary

EudraCT number	2009-011208-42
Trial protocol	NL GB
Global end of trial date	01 September 2014

Results information

Result version number	v1 (current)
This version publication date	25 March 2020
First version publication date	25 March 2020

Trial information

Trial identification

Sponsor protocol code	HTA083801

Additional study identifiers

ISRCTN number	ISRCTN92644181
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	Dr Rajendra Rai, Imperial College London, r.rai@imperial.ac.uk
Scientific contact	Dr Rajendra Rai, Imperial College London, r.rai@imperial.ac.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	01 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2014
Global end of trial reached?	Yes
Global end of trial date	01 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PRINCIPAL OBJECTIVE: To test the hypothesis that in women with unexplained recurrent miscarriages, progesterone (2 x 200mg pessaries, twice daily), started as soon as possible after a positive pregnancy test (and no later than 6 weeks gestation) and continued to 12 weeks of gestation, compared to placebo, increases live births beyond 24 completed weeks of pregnancy by at least 10%.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2009
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	Netherlands: 170
Country: Number of subjects enrolled	United Kingdom: 666
Worldwide total number of subjects	836
EEA total number of subjects	836

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	836
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 836 participants were randomized, exceeding the planned target of 790 participants, from 45 active centers (36 in the UK and nine in the Netherlands) over 41 months.

Pre-assignment

Screening details:

A total of 1568 participants were screened for eligibility and consented to take part in the PROMISE trial. Of these, 732 participants were excluded from randomization, the most common reasons being that they did not conceive naturally within 1 year or due to withdraw from the study.

Period 1

Period 1 title	Overall (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	Progresteron

Arm description:

Participants received progesterone at a dose of 400mg (that is, two capsules of Utrogestan® 200mg) taken vaginally twice daily (every morning and every evening) for the duration of treatment.

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

Dosage and administration details:

Micronised progesterone at a dose of 400mg (that is, two capsules of Utrogestan® 200mg) taken vaginally twice daily (every morning and every evening) for the duration of treatment.

Arm title	Placebo

Arm description:

Participants received placebo treatment

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

Dosage and administration details:

Two capsules of placebo capsules were taken vaginally twice daily (every morning and every evening) for the duration of treatment. Placebo capsules were composed of sunflower oil, soybean lecithin, gelatin, glycerol, titanium dioxide and purified water, encapsulated in the same form as the progesterone capsules, and identical in color, shape, and weight.

Number of subjects in period 1	Progresteron	Placebo
Started	404	432
Completed	387	423
Not completed	17	9
Consent withdrawn by subject	4	1
pregnancy end before treatment	10	7
progresteron before the treatment	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Progresteron
Reporting group description:	
Participants received progesterone at a dose of 400mg (that is, two capsules of Utrogestan® 200mg) taken vaginally twice daily (every morning and every evening) for the duration of treatment.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo treatment	

Reporting group values	Progresteron	Placebo	Total
Number of subjects	404	432	836
Age categorical			
Units: Subjects			
Women (18-35 years)	261	294	555
Women (35-39 years)	143	138	281
Age continuous			
Units: years			
median	32.9	32.5	
inter-quartile range (Q1-Q3)	29.3 to 36.3	28.9 to 35.9	-
Gender categorical			
Units: Subjects			
Female	404	432	836
Male	0	0	0
Maternal BMI			
Units: kg/m^2			
arithmetic mean	25.5	25.3	
standard deviation	± 5.1	± 5.1	-

End points

End points reporting groups

Reporting group title	Progresteron
Reporting group description:	
Participants received progesterone at a dose of 400mg (that is, two capsules of Utrogestan® 200mg) taken vaginally twice daily (every morning and every evening) for the duration of treatment.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo treatment	

Primary: Number of the live birth after at least 24 weeks of gestation compared to the total birth

End point title	Number of the live birth after at least 24 weeks of gestation compared to the total birth
End point description:	
End point type	Primary
End point timeframe:	
12 months	

End point values	Progresteron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	428		
Units: Percent	262	271		

Statistical analyses

Statistical analysis title	Live birth after at least 24 weeks of gestation
Statistical analysis description:	
Analyses based on the intention-to-treat principle.	
Comparison groups	Progresteron v Placebo
Number of subjects included in analysis	826
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	RR
Parameter estimate	Risk ratio (RR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.15

Secondary: Clinical pregnancy at 6–8 weeks	
End point title	Clinical pregnancy at 6–8 weeks
End point description: The presence of a gestational sac) at 6–8 weeks.	
End point type	Secondary
End point timeframe: 12 months	

End point values	Progresteron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	428		
Units: Number of clinical pregnancy	326	334		

Statistical analyses

Statistical analysis title	Clinical pregnancy at 6–8 weeks
Comparison groups	Progresteron v Placebo
Number of subjects included in analysis	826
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.16
Method	RR
Parameter estimate	Risk ratio (RR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.12

Secondary: Ongoing pregnancy at 12 weeks	
End point title	Ongoing pregnancy at 12 weeks
End point description: The presence of a fetal heartbeat at 12 weeks.	
End point type	Secondary
End point timeframe: 12 months	

End point values	Progresteron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	428		
Units: Number of ongoing pregnancy	267	277		

Statistical analyses

Statistical analysis title	Ongoing pregnancy at 12 weeks
Comparison groups	Progresteron v Placebo
Number of subjects included in analysis	826
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	RR
Parameter estimate	Risk ratio (RR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.14

Secondary: Number of Miscarriage

End point title	Number of Miscarriage

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Progresteron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	428		
Units: Number of Miscarriage	128	143		

Statistical analyses

Statistical analysis title	Miscarriage
Comparison groups	Progresteron v Placebo
Number of subjects included in analysis	826
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	RR
Parameter estimate	Risk ratio (RR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.17

Secondary: Number of Neonatal survival to 28 days	
End point title	Number of Neonatal survival to 28 days
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Progresteron	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	269		
Units: Number of Neonatal survival	260	269		

Statistical analyses

Statistical analysis title	Neonatal survival to 28 days
Comparison groups	Progresteron v Placebo
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	RR
Parameter estimate	Risk ratio (RR)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Progresteron
Reporting group description: Participants received progesterone at a dose of 400mg (that is, two capsules of Utrogestan® 200mg) taken vaginally twice daily (every morning and every evening) for the duration of treatment.	
Reporting group title	Placebo
Reporting group description: Participants received placebo treatment	

Serious adverse events	Progresteron	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 404 (0.25%)	0 / 432 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 404 (0.25%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Progresteron	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 404 (9.90%)	30 / 432 (6.94%)	
Nervous system disorders			
Neurological			
subjects affected / exposed	7 / 404 (1.73%)	4 / 432 (0.93%)	
occurrences (all)	7	4	
Blood and lymphatic system disorders			

Haematological subjects affected / exposed occurrences (all)	0 / 404 (0.00%) 0	1 / 432 (0.23%) 1	
Immune system disorders Allergy subjects affected / exposed occurrences (all)	2 / 404 (0.50%) 2	0 / 432 (0.00%) 0	
Gastrointestinal disorders Gastrointestinal subjects affected / exposed occurrences (all)	20 / 404 (4.95%) 20	14 / 432 (3.24%) 14	
Skin and subcutaneous tissue disorders Miscellaneous subjects affected / exposed occurrences (all)	8 / 404 (1.98%) 8	4 / 432 (0.93%) 4	
Renal and urinary disorders Urological subjects affected / exposed occurrences (all)	3 / 404 (0.74%) 3	4 / 432 (0.93%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2010	Adding new recruitment sites
10 January 2011	Adding new recruitment sites
23 March 2011	Change wording
06 April 2011	Adding new recruitment sites
20 April 2011	Adding new recruitment sites
20 April 2011	Wishaw General Hospital is going to be a PIC Patient Identification Centre only. Staffing issues make it difficult to function as a full research site.
03 May 2011	Pregnancy and delivery of trial drug - new wording. Some research centers have participants who live far away from the clinic, so returning solely to collect the study treatment is difficult for these individuals and may prevent them from taking part in the trial. The option of delivery directly from the trial pharmacy to their home address would make it possible for them to take part.
17 June 2011	Adding new recruitment sites
11 August 2011	Adding new recruitment sites
04 February 2013	Adding new recruitment sites

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27225013