Clinical trial results:
Does progesterone prophylaxis to prevent preterm labour improve outcome? - a randomised double blind placebo controlled trial (OPPTIMUM)

Summary

EudraCT number	2007-007950-77
Trial protocol	GB SE
Global end of trial date	31 December 2015

Results information

Result version number	v1 (current)
This version publication date	05 July 2020
First version publication date	05 July 2020
Summary attachment (see zip file)	Publication (PIIS0140-6736(16)00350-0 Full text in Lancet.pdf)

Trial information

Trial identification

Sponsor protocol code	OPPTIMUM

Additional study identifiers

ISRCTN number	ISRCTN14568373
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ETHICS: 08/MREOO/6, UKCRN: 4496, MRC FUNDER: G0700452, Grant No: 84982 - 09/800/27 , MHRA CTA: 22931/0009/001-0001 revised by MHRA to 01384/0208/

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Marise Bucukoglu, University of Edinburgh, marise.bucukoglu@ed.ac.uk
Scientific contact	Professor Jane Norman, University of Edinburgh, marise.bucukoglu@ed.ac.uk
Sponsor organisation name	NHS Lothian
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Dr Heather Charles Head of Research Governance NHS Lothian, NHS Lothian, ACCORD@nhslothian.scot.nhs.uk
Scientific contact	Dr Heather Charles Head of Research Governance NHS Lothian, NHS Lothian, ACCORD@nhslothian.scot.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	31 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2015
Global end of trial reached?	Yes
Global end of trial date	31 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In women at high risk of preterm labour, does prophylactic vaginal natural progesterone, 200mg daily from 22 – 34 weeks gestation, compared to placebo:

Protection of trial subjects:

We recruited pregnant women who were booked for their delivery at one of the hospitals participating in the study and who met the study eligibility criteria.

Case notes of pregnant women were reviewed for the patient's potential to participate and eligible patients were informed of the study at routine antenatal appointments or by the research midwife or another member of the hospital or research team by telephone or direct mailing of the participant invitation or the current patient information sheet.

Women given information about the study were offered at least 24 hours to read the patient information sheet and invited to consider participation.

Background therapy:

All women fulfilling the inclusion criteria and consented were tested for fetal fibrenectin (ffn). Those with a positive screening (fFN) test between 22+0 and 24+0 weeks, were eligible for randomisation.

Additionally, those who have a previous spontaneous labour resulting in a preterm birth ≤ 34 weeks gestation (by any mode) or short cervix in index pregnancy, defined as cervical length ≤ 25mm were eligible for randomisation to progesterone or placebo even with a negative fFN test.

Evidence for comparator: -

Actual start date of recruitment	03 December 2008
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	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 1221
Worldwide total number of subjects	1228
EEA total number of subjects	1228

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)	1228
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All eligible women will be invited to participate in this part of the study. The trial will be explained in detail to the patient and any questions they have will be answered. Those who complete the consent form will undergo fibronectin testing at 22+0 to 24+0weeks gestation.

Pre-assignment

Screening details:

Period 1: 5833 pregnant women were tested for fibronectin. 4605 were excluded from randomisation 1228 were randomised to either progesterone or matching placebo.

Period 2: We assesed Neonatal outcomes 1176 babies of women randomised and who were willing.

Period 3 We conducted 919 childhood assesments age 2 years of women randomised.

Period 1

Period 1 title	Obstetric phase
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:

The IMP (progesterone) was supplied free of charge to all sites, directly by the manufacturer, Laboratories Besins International. Placebo capsules were identical to active treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Progesterone

Arm description:

Utrogestan (Progesterone) 200mg soft capsules

Arm type	Active comparator
Investigational medicinal product name	Progesterone
Investigational medicinal product code	PL16468/0001
Other name	Uterogestan
Pharmaceutical forms	Pessary
Routes of administration	Vaginal use

Dosage and administration details:

Utrogestan (Progesterone) 200 mg soft capsules or placebo will be prescribed at Visit 2 to be inserted once daily vaginally at bedtime for up to 12 weeks.

Arm title	Placebo

Arm description:

Placebo pessary

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

Dosage and administration details:

200mg Matching placebo dministered once daily

Number of subjects in period 1	Progesterone	Placebo
Started	618	610
Completed	600	597
Not completed	18	13
Consent withdrawn by subject	12	10
Lost to follow-up	6	2
Obstetric data missing	-	1

Period 2

Period 2 title	Neonatal
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Progesterone

Arm description:

Utrogestan (Progesterone) 200mg soft capsules

Arm type	Active comparator
Investigational medicinal product name	Progesterone
Investigational medicinal product code	PL16468/0001
Other name	Uterogestan
Pharmaceutical forms	Pessary
Routes of administration	Vaginal use

Dosage and administration details:

Utrogestan (Progesterone) 200 mg soft capsules or placebo will be prescribed at Visit 2 to be inserted once daily vaginally at bedtime for up to 12 weeks.

Arm title	Placebo

Arm description:

Placebo pessary

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

Dosage and administration details:

200mg Matching placebo dministered once daily

Number of subjects in period 2	Progesterone	Placebo
Started	618	610
Completed	589	587
Not completed	29	23
Consent withdrawn by subject	15	18
Lost to follow-up	14	5

Period 3

Period 3 title	Paediatric
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Women were Blinded. Treatment was not unblinded throughout the follow up period

Arms

Are arms mutually exclusive?	No
Arm title	Progesterone

Arm description:

Utrogestan (Progesterone) 200mg soft capsules

Arm type	Active comparator
Investigational medicinal product name	Progesterone
Investigational medicinal product code	PL16468/0001
Other name	Uterogestan
Pharmaceutical forms	Pessary
Routes of administration	Vaginal use

Dosage and administration details:

Utrogestan (Progesterone) 200 mg soft capsules or placebo will be prescribed at Visit 2 to be inserted once daily vaginally at bedtime for up to 12 weeks.

Arm title	Placebo

Arm description:

Placebo pessary

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

Dosage and administration details:

200mg Matching placebo dministered once daily

Number of subjects in period 3	Progesterone	Placebo
Started	618	610
Completed	430	439
Not completed	188	171
Consent withdrawn by subject	47	42
Lost to follow-up	141	129

Baseline characteristics

Reporting groups	
Reporting group title	Progesterone
Reporting group description:	
Utrogestan (Progesterone) 200mg soft capsules	
Reporting group title	Placebo
Reporting group description:	
Placebo pessary	

Reporting group values	Progesterone	Placebo	Total
Number of subjects	618	610	1228
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	31.4	31.5	
standard deviation	± 5.7	± 5.6	-
Gender categorical			
Units: Subjects			
Female	618	610	1228
Male	0	0	0

End points

End points reporting groups

Reporting group title	Progesterone
Reporting group description: Utrogestan (Progesterone) 200mg soft capsules	
Reporting group title	Placebo
Reporting group description: Placebo pessary	
Reporting group title	Progesterone
Reporting group description: Utrogestan (Progesterone) 200mg soft capsules	
Reporting group title	Placebo
Reporting group description: Placebo pessary	
Reporting group title	Progesterone
Reporting group description: Utrogestan (Progesterone) 200mg soft capsules	
Reporting group title	Placebo
Reporting group description: Placebo pessary	

Primary: Fetal Death or delivery before 34 weeks' gestation

End point title	Fetal Death or delivery before 34 weeks' gestation
End point description:	
End point type	Primary
End point timeframe: Birth/ Delivery	

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	618	610		
Units: number				
number (not applicable)	504	489		

Statistical analyses

Statistical analysis title	Death or delivery before 34 weeks' gestation
Comparison groups	Progesterone v Placebo

Number of subjects included in analysis	1228
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	Regression, Linear

Notes:

[1] - Intention to treat

Primary: Death, brain injury or severe chronic lung disease

End point title	Death, brain injury or severe chronic lung disease

End point description:

End point type	Primary

End point timeframe:

Neonatal period

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	589[2]	587[3]		
Units: Number				
number (not applicable)	46	62		

Notes:

[2] - Nobs (Nmiss) 589 (27)
No, n (%) 543 (92.2)
Yes, n (%) 46 (7.8)
[3] - Nobs, n 587 (23)
NO, n (%) 525 (89.4)
YES, n (%) 62 (10.6)

Statistical analyses

Statistical analysis title	Death or delivery before 34 weeks' gestation
Comparison groups	Progesterone v Placebo
Number of subjects included in analysis	1176
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.05
Method	Regression, Linear

Notes:

[4] - Intention to Treat

Primary: Bayley-III cognitive composite score at 2 years

End point title	Bayley-III cognitive composite score at 2 years

End point description:

End point type	Primary

End point timeframe:

Age 2 years (adjusted)

End point values	Progesterone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410[5]	423[6]		
Units: Number				
arithmetic mean (standard deviation)	99.7 (± 14.7)	99.5 (± 15.0)		

Notes:

[5] - Nobs (Nmiss) 410 (206)
Mean (SD) 99.7 (14.7)
Median (IQR) 100.0 (90.0–110.0)
[6] - Nobs (Nmiss) 423 (187)
Mean (SD) 99.5 (15.0)
Median (IQR) 100.0 (90.0–105.0)

Statistical analyses

Statistical analysis title	Bayley-III cognitive composite score at 2 years
Comparison groups	Progesterone v Placebo
Number of subjects included in analysis	833
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.05
Method	Regression, Linear

Notes:

[7] - Intention to treat

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Recorded from the time a participant is randomized to treatment until 30 days after stopping taking study drug (study observational visit) and until pregnancy outcome (28 days after delivery.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The Investigators were requested to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) and record all relevant information in the patient notes, the eCRF only if the AE meets the criteria of serious was it reported to the Sponsors.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2008	Ethics requested updates to docs in appoval letter
21 April 2008	Change sponsor
22 September 2008	Protocol redesigned layout to comply with NEW sponsor requirements
03 June 2009	Clarification of inclusion/exclusion criteria and items previously noted as TBC included.
15 October 2009	Correction of Typographical errors including the inclusion criteria which should have been aged16 as per previous ethics documentation. Removal of stratification Para 5.5
07 April 2010	Change in IMP excipient,
01 June 2010	Change to exclusion criteria and identifying patients
12 July 2010	To expand recruitment criteria (including fFN-ve women)
24 April 2011	Change exclusion,
16 February 2012	Background literature updated, Information on pilot studies removed Para 9.1 Sample size revised to 1250 Para 9.2.2 Deletion of formal plan for Health economic analysis (although collection of some economic data remains part of the study protocol)
04 October 2013	Revised Protocol V15_04 October 2013 to amend paras 7.2.7 Neonatal/Child Assessments (Section: 'Child Assessment (at 2 years +/- 8 weeks)'

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/29945711

http://www.ncbi.nlm.nih.gov/pubmed/26921136

http://www.ncbi.nlm.nih.gov/pubmed/22866909