Clinical trial results:
A Proof of Principle, Double-Blind, Randomised Placebo-Controlled, Multi-centre Trial of pravaStatin to Ameliorate Early Onset Pre-eclampsia

Summary

EudraCT number	2009-012968-13
Trial protocol	GB
Global end of trial date	09 September 2014

Results information

Result version number	v1 (current)
This version publication date	12 July 2018
First version publication date	12 July 2018

Trial information

Trial identification

Sponsor protocol code	UCL08/0350

Additional study identifiers

ISRCTN number	ISRCTN23410175
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	149 Tottenham Court Road, London, United Kingdom, W1T 7DN
Public contact	Anne Downey, University College London, a.downey@ucl.ac.uk
Scientific contact	Anne Downey, University College London, a.downey@ucl.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	22 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2014
Global end of trial reached?	Yes
Global end of trial date	09 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the trial is to establish whether pravastatin will lead to a significant reduction of circulating anti-angiogenic factors in women with early-onset pre-eclampsia. To test this hypothesis, we will ask the following questions:
1. Does pravastatin cause a greater inhibition of circulating anti-angiogenic factors in women with early-onset pre-eclampsia compared with placebo?
2. Are there any beneficial or adverse clinical effects to the mother or the baby following gestational exposure to pravastatin?
3. If pravastatin appears to safely inhibit circulatating anti-angiogenic factors, how best can a substantive trial/health technology assessment be undertaken to develop guidance for routine use of statins to prevent or ameliorate pre-eclampsia?

Protection of trial subjects:

No specific measures

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2011
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: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	62
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited and randomised into the trial on the 18-Jun-2011 and the last patient was randomised into the trial on 30-Jun-2014.
The study was open in the UK only and was open in 16 centres.

Pre-assignment

Screening details:

There were 388 women screened in order to randomise 62 women.

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, Assessor

Blinding implementation details:

Overencapsulated IMP and matching placebo

Arms

Are arms mutually exclusive?	Yes
Arm title	Pravastatin

Arm description:

Pravastatin

Arm type	Experimental
Investigational medicinal product name	Pravastatin
Investigational medicinal product code	IMP1
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

40mg daily until delivery

Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

Daily until delivery

Number of subjects in period 1	Pravastatin	Placebo
Started	30	32
Completed	30	32

Baseline characteristics

Reporting groups	
Reporting group title	Pravastatin
Reporting group description: Pravastatin	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Pravastatin	Placebo	Total
Number of subjects	30	32	62
Age categorical Units: Subjects			
Adults	30	32	62
Age continuous Units: years			
arithmetic mean	32.4	30.4	
standard deviation	± 5.6	± 6.3	-
Gender categorical			
Sex, as subjects all pregnant			
Units: Subjects			
Female	30	32	62
Male	0	0	0
Gestational age at diagnosis			
Gestational age of fetus, in weeks, at diagnosis of severe pre-eclampsia. Eligible if <32+6 weeks.			
Units: Subjects			
<30 weeks	23	24	47
>= 30 weeks	7	8	15
Smoking status at diagnosis			
Self-declared smoking status			
Units: Subjects			
Smoker	2	1	3
Stopped smoking when became pregnant	1	1	2
Non-smoker	27	30	57
Severity of pre-eclampsia at randomisation			
All Using internationally recognised standard definitions, two categories of severity were defined: 1. Blood pressure >140mmHg systolic or 90mmHg diastolic but <160mmHg and <110mmHg respectively 2. Blood pressure ≥160mmHg systolic or 110mmHg diastolic			
Units: Subjects			
Blood pressure >140mmHg systolic or 90mmHg diastol	13	14	27
Blood pressure ≥160mmHg systolic or 110mmHg diasto	17	18	35

Subject analysis sets	
Subject analysis set title	Pravastatin
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects analysed according to the arm to which they were randomised, regardless of compliance.	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects analysed according to the arm to which they were randomised, regardless of compliance.	

Reporting group values	Pravastatin	Placebo	
Number of subjects	30	32	
Age categorical Units: Subjects			
Adults	62		
Age continuous Units: years			
arithmetic mean	32.4	30.4	
standard deviation	± 5.6	± 6.3	
Gender categorical			
Sex, as subjects all pregnant			
Units: Subjects			
Female	30	32	
Male	0	0	
Gestational age at diagnosis			
Gestational age of fetus, in weeks, at diagnosis of severe pre-eclampsia. Eligible if <32+6 weeks.			
Units: Subjects			
<30 weeks	23	24	
>= 30 weeks	7	8	
Smoking status at diagnosis			
Self-declared smoking status			
Units: Subjects			
Smoker	2	1	
Stopped smoking when became pregnant	1	1	
Non-smoker	27	30	
Severity of pre-eclampsia at randomisation			
All Using internationally recognised standard definitions, two categories of severity were defined: 1. Blood pressure >140mmHg systolic or 90mmHg diastolic but <160mmHg and <110mmHg respectively 2. Blood pressure ≥160mmHg systolic or 110mmHg diastolic			
Units: Subjects			
Blood pressure >140mmHg systolic or 90mmHg diastol	13	14	
Blood pressure ≥160mmHg systolic or 110mmHg diasto	17	18	

End points

End points reporting groups

Reporting group title	Pravastatin
Reporting group description: Pravastatin	
Reporting group title	Placebo
Reporting group description: Placebo	
Subject analysis set title	Pravastatin
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All subjects analysed according to the arm to which they were randomised, regardless of compliance.	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All subjects analysed according to the arm to which they were randomised, regardless of compliance.	

Primary: sFLT-1

End point title	sFLT-1
End point description:	
End point type	Primary
End point timeframe: First 3 days after randomisation	

End point values	Pravastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[1]	29[2]		
Units: ng/ml				
arithmetic mean (standard deviation)	8.52 (± 4.8)	12.24 (± 6.39)		

Notes:

[1] - Number of subjects providing at least 1 sample/ datapoint

[2] - Number of subjects providing at least 1 sample/ datapoint

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Placebo v Pravastatin
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.6
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first administration of trial treatment to 6 weeks post-delivery	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	11
Reporting groups	
Reporting group title	Pravastatin
Reporting group description: Pravastatin	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	Pravastatin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)	5 / 29 (17.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Hypertensive emergency	Additional description: Uncontrolled and/or exacerbation of hypertension		
subjects affected / exposed	3 / 30 (10.00%)	3 / 29 (10.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Haemorrhage in pregnancy	Additional description: Antepartum haemorrhage requiring Caesarean delivery		
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (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			
Haematoma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Liver function test abnormal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Postpartum neurosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (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			
Postpartum sepsis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	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	Pravastatin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)	9 / 29 (31.03%)	
Vascular disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 30 (6.67%)	4 / 29 (13.79%)	
occurrences (all)	2	4	
Dizziness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Eye disorders			

Photopsia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Vomiting in pregnancy			
subjects affected / exposed	2 / 30 (6.67%)	3 / 29 (10.34%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	0 / 30 (0.00%)	5 / 29 (17.24%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 30 (0.00%)	3 / 29 (10.34%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2011	Version 3.1 from AM01 (modification)
22 November 2011	Version 4.0 from AM02
16 April 2012	Version 5.0 from AM03
19 July 2012	Version 6.0 from AM04
18 January 2013	Version 7.0 from AM05

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported