Clinical trial results:
Combined Multi-Marker Screening and Randomised Patient Treatment with Aspirin for Evidence-based Pre-eclampsia Prevention

Summary

EudraCT number	2013-003778-29
Trial protocol	GB IT BE GR
Global end of trial date	03 November 2016

Results information

Result version number	v1 (current)
This version publication date	30 June 2018
First version publication date	30 June 2018

Trial information

Trial identification

Sponsor protocol code	CTU/2013/064

Additional study identifiers

ISRCTN number	ISRCTN13633058
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1140-4837

Notes:

Sponsors

Sponsor organisation name	Comprehensive Clinical Trials Unit at UCL
Sponsor organisation address	Institute of Clinical Trials and Methodology, 90 High Holborn, London, United Kingdom, WC1V 6LJ
Public contact	CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk
Scientific contact	CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@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	02 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2016
Global end of trial reached?	Yes
Global end of trial date	03 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine if the use of low-dose aspirin starting at 11-14 weeks gestation in women at increased risk for pre-eclampsia (high blood pressure) can reduce the incidence and severity of this complication.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, UCL CCTU Standard Operating Procedures (SOPs), the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites complied with the approved protocol, UCL CCTU SOPs, the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable) and other national and local applicable regulations.

Irrespective of indications, there were no dose modifications. One fixed dose of 150 mg aspirin or placebo was used. This dosage was carefully selected based on aspirin pharmacology.

Protocol pre-defined reasons for discontinuation of trial medication were in place in the event of participants experiencing: unacceptable treatment toxicity or adverse event; inter-current illness that prevents further treatment; any change in the participant’s condition that in the clinician’s opinion justifies the discontinuation of treatment; protocol violations; cure; administrative reasons or other reasons.

All participants could choose to discontinue trial treatment at any time, without giving a reason, without penalty or loss of benefits to which they would otherwise be entitled.

Investigation and treatment of adverse events were as per NHS standard of care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2014
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	Israel: 2
Country: Number of subjects enrolled	Spain: 356
Country: Number of subjects enrolled	United Kingdom: 1227
Country: Number of subjects enrolled	Belgium: 88
Country: Number of subjects enrolled	Greece: 53
Country: Number of subjects enrolled	Italy: 50

Worldwide total number of subjects	1776
EEA total number of subjects	1774

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)	1776
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 13 maternity hospitals in England, Spain, Italy, Belgium, Greece and Israel. All women attending for a routine hospital visit at 11+0 to 13+6 weeks of gestation in the participating hospitals are offered screening for preeclampsia by the same algorithm.

Pre-assignment

Screening details:

High-risk (>1 in 100) for preterm preeclampsia.

Period 1

Period 1 title	Randomization (overall period)
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:

Eligible women were randomly assigned, in a 1:1 ratio, with the use of a web-based system (Sealed Envelope, London, UK), to receive either aspirin or placebo and in the random-sequence generation there was stratification according to participating center. The placebo and aspirin tablets were manufactured by Actavis UK Ltd, Devon, UK and were packaged, labelled, stored and distributed by Mawdsley Brooks and Co, Salford, UK.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aspirin

Arm description:

150mg of Aspirin taken at bedtime commencing between 11-14 weeks gestation, depending on recruitment,... more

Arm type	Experimental
Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150mg taken orally at bedtime

Arm title	Placebo

Arm description:

Identical in appearance and packaging to experimental treatment.

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

Dosage and administration details:

Matched placebo taken at bedtime.

Number of subjects in period 1	Aspirin	Placebo
Started	878	898
Completed	798	822
Not completed	80	76
Consent withdrawn by subject	78	74
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Aspirin
Reporting group description:	
150mg of Aspirin taken at bedtime commencing between 11-14 weeks gestation, depending on recruitment,... more	
Reporting group title	Placebo
Reporting group description:	
Identical in appearance and packaging to experimental treatment.	

Reporting group values	Aspirin	Placebo	Total
Number of subjects	878	898	1776
Age categorical Units: Subjects			
Age continuous Units: years			
median	31.5	31.4	
inter-quartile range (Q1-Q3)	27.3 to 35.8	26.9 to 35.8	-
Gender categorical Units: Subjects			
Female	878	898	1776
Male	0	0	0
Race or ethnic group Units: Subjects			
White	529	560	1089
Black	208	202	410
South Asian	38	37	75
East Asian	13	16	29
Mixed race	12	9	21
Withdrew consent	78	74	152
Method of conception Units: Subjects			
Natural	749	781	1530
Assisted by ovulation drugs	6	7	13
In virto fertilization	45	36	81
Withdrew consent	78	74	152
Smoking Units: Subjects			
Smoker	57	60	117
None smoker	743	764	1507
Withdrew consent	78	74	152
Chronic hypertension Units: Subjects			
Yes	49	61	110
No	751	763	1514
Withdrew consent	78	74	152
Systemic lupus erythematosus			

Units: Subjects			
Yes	3	1	4
No	797	823	1620
Withdrew consent	78	74	152
Antiphospholipid syndrome Units: Subjects			
Yes	2	2	4
No	798	822	1620
Withdrew consent	78	74	152
Diabetes mellitus Units: Subjects			
Type 1	7	2	9
Type 2	8	8	16
None	785	814	1599
Withdrew consent	78	74	152
Obstetrical history Units: Subjects			
Nulliparous	548	545	1093
Multiparous without preeclampsia	165	195	360
Multiparous with preeclampsia	87	84	171
Withdrew consent	78	74	152
Gestational age at randomization Units: Weeks			
median	12.7	12.6	
inter-quartile range (Q1-Q3)	12.3 to 13.1	12.3 to 13.0	-
Body-mass index Units: Weight in kg/square of height m			
median	26.7	26.5	
inter-quartile range (Q1-Q3)	23.3 to 31.1	23.0 to 31.5	-
Interval from last pregnancy Units: years			
median	4.2	4.6	
inter-quartile range (Q1-Q3)	2.5 to 7.0	2.9 to 7.5	-

End points

End points reporting groups

Reporting group title	Aspirin
Reporting group description:	
150mg of Aspirin taken at bedtime commencing between 11-14 weeks gestation, depending on recruitment,... more	
Reporting group title	Placebo
Reporting group description:	
Identical in appearance and packaging to experimental treatment.	

Primary: Preeclampsia with delivery before 37 week

End point title	Preeclampsia with delivery before 37 week
End point description:	
End point type	Primary
End point timeframe:	
Delivery	

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	798	822		
Units: Subjects				
Yes	13	35		
No	785	787		

Statistical analyses

Statistical analysis title	Mixed effects logistic regression
Statistical analysis description:	
Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).	
Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.38

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.74

Secondary: Adverse outcomes with delivery before 37 weeks

End point title	Adverse outcomes with delivery before 37 weeks

End point description:

Delivery before 37 weeks gestation associated with preeclampsia, gestational hypertension, miscarriage, stillbirth, small-for-gestational-age abruption or spontaneous delivery. Please see attached chart for details.

End point type	Secondary

End point timeframe:

Delivery before 37 weeks gestation

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	798	822		
Units: Subjects				
Yes	79	116		
No	719	706		

Attachments (see zip file)	Odds ratios (aspirin/placebo) with 99% CIs. /Adverse

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).

Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.46
upper limit	1.03

Secondary: Adverse outcomes with delivery before 34 weeks

End point title	Adverse outcomes with delivery before 34 weeks

End point description:

Delivery before 34 weeks gestation associated with preeclampsia, gestational hypertension, miscarriage, stillbirth, small-for-gestational-age abruption or spontaneous delivery.

Please see attached chart for details.

End point type	Secondary

End point timeframe:

Adverse outcomes before 34 weeks.

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	798	822		
Units: Subjects				
Yes	32	53		
No	766	769		

Attachments (see zip file)	Odds ratios (aspirin/placebo) with 99% CIs. /Adverse

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).

Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.62
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.34
upper limit	1.14

Secondary: Adverse outcomes with delivery at 37 weeks or later

End point title	Adverse outcomes with delivery at 37 weeks or later

End point description:

Adverse outcomes with delivery at 37 weeks gestation or later associated with preeclampsia, gestational hypertension, stillbirth, small-for-gestational-age abruption or spontaneous delivery.

Please see attached chart for details.

End point type	Secondary

End point timeframe:

Delivery at 37 weeks gestation or later.

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	798	822		
Units: Subjects				
Yes	178	171		
No	620	651		

Attachments (see zip file)	Odds ratios (aspirin/placebo) with 99% CIs. /Adverse

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).

Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.82
upper limit	1.54

Secondary: All stillbirths or deaths

End point title	All stillbirths or deaths

End point description:

Miscarriages, stillbirths or deaths. For breakdown by preeclampsia, small-for-gestation and placental abruption or bleeding see chart.

End point type	Secondary

End point timeframe:

Miscarriages and births.

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	798	822		
Units: Subjects				
Yes	8	14		
No	790	808		

Attachments (see zip file)	Odds ratios (aspirin/placebo) with 99% Cis./Neonatal

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).

Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.59
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.19
upper limit	1.85

Secondary: Death or complications

End point title	Death or complications

End point description:

Death, miscarriage or complications from intraventricular hemorrage of grade II or above, sepsis with confirmed bacteremia in cultures, anemia resulting in blood transfusion, respitoratory distress syndrome treated with surfactant and ventilation or necrotizing enterocolitis resulting in surgery.

See chart for breakdown.

End point type	Secondary

End point timeframe:

Miscarriage or birth.

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	798	822		
Units: Subjects				
Yes	32	48		
No	766	774		

Attachments (see zip file)	Odds ratios (aspirin/placebo) with 99% CIs./Neonatal

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).

Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.37
upper limit	1.27

Secondary: Poor fetal growth: Birth weight below 3rd percentile

End point title	Poor fetal growth: Birth weight below 3rd percentile

End point description:

End point type	Secondary

End point timeframe:

Weight at birth for babies born after 24 weeks gestation.

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	785[1]	807[2]		
Units: Subjects				
Yes	57	63		
No	728	744		

Notes:

[1] - Birth weight for deliveries before 24 weeks was not recorded.

[2] - Birth weight for deliveries before 24 weeks was not recorded.

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).

Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1592
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.57
upper limit	1.51

Secondary: Poor fetal growth: Birth weight below 5th percentile

End point title	Poor fetal growth: Birth weight below 5th percentile

End point description:

End point type	Secondary

End point timeframe:

Weight at birth.

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	785[3]	807[4]		
Units: Subjects				
Yes	82	96		
No	703	744		

Notes:

[3] - Birth weight for deliveries before 24 weeks was not recorded.

[4] - Birth weight for deliveries before 24 weeks was not recorded.

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:	
Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).	
Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1592
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.86
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.57
upper limit	1.3

Secondary: Poor fetal growth: Birth weight below 10th percentile

End point title	Poor fetal growth: Birth weight below 10th percentile
End point description:	
End point type	Secondary
End point timeframe:	
Weight at birth.	

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	785[5]	807[6]		
Units: Subjects				
Yes	148	187		
No	637	620		

Notes:

[5] - Birth weight for deliveries before 24 weeks was not recorded.

[6] - Birth weight for deliveries before 24 weeks was not recorded.

Statistical analyses

Statistical analysis title	Mixed effects logistic regression.
Statistical analysis description:	
Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).	
Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1592
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.77

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.56
upper limit	1.06

Secondary: Admission to intensive care unit

End point title	Admission to intensive care unit

End point description:

End point type	Secondary

End point timeframe:

Birth.

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	798	822		
Units: Subjects				
Yes	48	54		
No	750	768		

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).

Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.55
upper limit	1.59

Secondary: Ventilation with positive airway pressure intubation

End point title	Ventilation with positive airway pressure intubation

End point description:

End point type	Secondary

End point timeframe:

Birth.

End point values	Aspirin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	798	822		
Units: Subjects				
Yes	37	46		
No	761	776		

Statistical analyses

Statistical analysis title	Mixed effects logistic regression

Statistical analysis description:

Logistic regression adjusted for participating center (random effect) and logit of risk at screening (fixed effect).

Comparison groups	Aspirin v Placebo
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.85
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.47
upper limit	1.52

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period for adverse events reporting was from the time of first dose until 30 days post final IMP administration. The participants were be followed up by a telephone interview 30 days after the last dose of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Aspirin
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Aspirin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 878 (1.48%)	26 / 898 (2.90%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Surgical and medical procedures			
Maternal appendicitis requiring surgery			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	2 / 898 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maternal cholangitis requiring surgery			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 878 (0.11%)	0 / 898 (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			
Fetal chromosomal abnormality: Trisomy 21			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 878 (0.34%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal chromosomal abnormality: Klinefelter syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal chromosomal abnormality: Microdeletion chromosome 16			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal chromosomal abnormality: Microdeletion chromosome 15			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal chromosomal abnormality: Di George syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 878 (0.11%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Intracranial hemorrhage due to traumatic delivery			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Ventriculomegaly, talipes, deformed hand			

subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Cleft lip			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Congenital diaphragmatic hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	2 / 898 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Tetralogy of Fallot, Dandy Walker malformation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Tetrallogy of Fallot			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 878 (0.11%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Ventricular septal defect			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 878 (0.23%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maternal death due to pulmonary embolism			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular septal defect and right aortic arch			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Pulmonary stenosis and ambiguous genitalia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Mild pulmonary stenosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Multicyclic dysplastic kidney unilateral			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 878 (0.23%)	0 / 898 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Duplex kidney unilateral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Renal agenesis unilateral			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 878 (0.11%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Absent right forearm			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Talipes equinivarus bilateral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 878 (0.11%)	0 / 898 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Rectal stenosis requiring surgery			
subjects affected / exposed	1 / 878 (0.11%)	0 / 898 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Cutaneous angioma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defect: Hypoplastic left heart syndrome (fetal)			
subjects affected / exposed	0 / 878 (0.00%)	2 / 898 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal structural defects: Coartcation of the aorta	Additional description: Withdrawal from trial.		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 878 (0.11%)	0 / 898 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal chromosomal abnormalities: Di George Syndrome	Additional description: Withdrawal from trial.		
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Maternal abdominal pain with prolonged hospital stay (4d)			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 898 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aspirin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	207 / 878 (23.58%)	210 / 898 (23.39%)	
Nervous system disorders			
Headache and/or dizziness			
subjects affected / exposed	78 / 878 (8.88%)	74 / 898 (8.24%)	
occurrences (all)	78	74	
Blood and lymphatic system disorders			
Vaginal bleeding			
subjects affected / exposed	29 / 878 (3.30%)	21 / 898 (2.34%)	
occurrences (all)	29	21	
Nasal bleeding			
subjects affected / exposed	16 / 878 (1.82%)	27 / 898 (3.01%)	
occurrences (all)	16	27	
Other bleeding			
subjects affected / exposed	7 / 878 (0.80%)	5 / 898 (0.56%)	
occurrences (all)	7	5	
Anemia			

subjects affected / exposed	4 / 878 (0.46%)	7 / 898 (0.78%)	
occurrences (all)	4	7	
General disorders and administration site conditions			
Infections			
subjects affected / exposed	17 / 878 (1.94%)	17 / 898 (1.89%)	
occurrences (all)	17	17	
Pain in chest, back or limbs			
subjects affected / exposed	10 / 878 (1.14%)	10 / 898 (1.11%)	
occurrences (all)	10	10	
Pruritus			
subjects affected / exposed	8 / 878 (0.91%)	8 / 898 (0.89%)	
occurrences (all)	8	9	
Peripheral edema			
subjects affected / exposed	8 / 878 (0.91%)	6 / 898 (0.67%)	
occurrences (all)	8	6	
Shortness of breath			
subjects affected / exposed	5 / 878 (0.57%)	6 / 898 (0.67%)	
occurrences (all)	5	6	
Visual disturbance			
subjects affected / exposed	5 / 878 (0.57%)	4 / 898 (0.45%)	
occurrences (all)	5	4	
Palpitations			
subjects affected / exposed	6 / 878 (0.68%)	3 / 898 (0.33%)	
occurrences (all)	6	3	
Paraesthesia			
subjects affected / exposed	6 / 878 (0.68%)	2 / 898 (0.22%)	
occurrences (all)	6	2	
Fatigue or weakness			
subjects affected / exposed	2 / 878 (0.23%)	3 / 898 (0.33%)	
occurrences (all)	2	3	
Other			
subjects affected / exposed	13 / 878 (1.48%)	18 / 898 (2.00%)	
occurrences (all)	13	18	
Gastrointestinal disorders			

Nausea and/or vomiting			
subjects affected / exposed	40 / 878 (4.56%)	36 / 898 (4.01%)	
occurrences (all)	40	36	
Abdominal and/or pelvic pain			
subjects affected / exposed	28 / 878 (3.19%)	33 / 898 (3.67%)	
occurrences (all)	28	33	
Dyspepsia and/or heartburn			
subjects affected / exposed	20 / 878 (2.28%)	22 / 898 (2.45%)	
occurrences (all)	20	22	
Diarrhoea			
subjects affected / exposed	9 / 878 (1.03%)	6 / 898 (0.67%)	
occurrences (all)	9	6	
Constipation			
subjects affected / exposed	3 / 878 (0.34%)	4 / 898 (0.45%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Skin rash			
subjects affected / exposed	9 / 878 (1.03%)	11 / 898 (1.22%)	
occurrences (all)	9	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2014	Protocol updated to v2.5 08 May 2014 to include the following: criteria for screening updated from 11-13 weeks gestation to 11-13 weeks gestation or a crown-rump length of 45-84mm; window for randomisation visits has been extended from 11-13 to 11-14 weeks gestation; extension of follow-up visit 2 window on screen negative participants from 32-34 to 30-37 weeks gestation; and other administrative changes and clarifications. Regulatory authorities receiving and approving substantial amendment: UK, Belgium and Italy.
25 November 2014	Protocol updated to v3.0 21 Oct 2014 to include the following: introduction of the Screening Quality Study (SQS) to precede the main trial; eligibility criteria updated to denote those criteria which are applicable to the SQS and screening stage of the main trial; and removal of interim analysis as no longer feasible due to reduced recruitment timelines for the main trial. Regulatory authorities receiving and approving substantial amendment: UK, Belgium, Spain and Italy.
11 June 2015	Protocol updated to v4.0, 16 Apr 2015 to include the following: clarification of exclusion criteria in relation to aspirin administration; amendments to IMP supply arrangements; extension of first clinical visit window to coincide with those which form part of routine clinical care at more study sites; the minimum recruitment period for the Screening Quality Study amended from three months to one to three months (dependent on sites' performance); sites being given the option of dispensing IMP from ward where it is not practical to dispense directly from pharmacy; compliance testing by blood test will now be conducted on all RCT participants rather than 10%; safety reporting period amended from ceasing 30 days after the last IMP administration to 30 days after the last IMP administration for events relating directly to participants and 30 days after delivery or the expected date of delivery, whichever is the latter, for congenital abnormalities/birth defects identified in participant's baby; clarification of trial closure; and clarification of exceptions to SAE reporting (miscarriage added as exception). Regulatory authorities receiving and approving substantial amendment: UK, Belgium, Spain and Italy.
25 November 2015	Protocol updated to v5.0 23 Sep 2015 to incorporate the addition of a sub-study at UK study sites only to evaluate maternal cardiac function by a non-invasive method and other minor changes throughout the protocol. Regulatory authorities receiving and approving substantial amendment: UK.
01 March 2016	Details: Protocol updated to v6.0 25 Jan 2016 to include the following: clarification of secondary objectives and secondary outcomes; changes to safety reporting (non-serious AE/AR no longer reported to UCL CCTU and introduction of reporting of protocol-defined exceptions to SAE to UCL CCTU); changes to compliance testing (cut-offs defined for assessment of compliance testing by tablet count and biochemical assessment of compliance by blood test changed to post hoc analysis); and an increase in the sample size from 1684 to 1760. Regulatory authorities receiving and approving substantial amendment: UK, Belgium, Spain, Italy and Greece.

27 July 2016	Protocol updated to v 7.0 07 Jul 2016 to include changes to the type of analysis and statistical tests which will be performed on main ASPRE trial data, collection of additional samples of placenta and cord blood for the cardiac sub-study at King's College Hospital and minor administrative changes throughout the protocol. Regulatory authorities receiving and approving substantial amendment: UK, Belgium, Spain, Italy and Greece.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 June 2014	A temporary halt was placed on the trial in June 2014 due to administrative problems with the supply of investigational medicinal product (IMP). The trial was restarted in July 2015 following securing an alternative IMP supplier and recruitment was completed in April 2016. The temporary halt followed the recruitment of 56 participants to the pilot study, the start of the randomised control trial, at King's College Hospital in the United Kingdom. The manufacture and composition of the IMP were the same throughout the trial, and the women who were enrolled during 2014 were included in the trial population.	16 July 2015

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28657417