Clinical trial results:
ANODE: a randomised controlled trial of prophylactic ANtibiotics to investigate the prevention of infection following Operative vaginal DElivery.

Summary

EudraCT number	2015-000872-89
Trial protocol	GB
Global end of trial date	12 November 2018

Results information

Result version number	v1 (current)
This version publication date	08 November 2019
First version publication date	08 November 2019

Trial information

Trial identification

Sponsor protocol code	MK001

Additional study identifiers

ISRCTN number	ISRCTN11166984
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	CTRG, Joint Research Office, Boundary Brook House, Churchill Drive, Oxford, United Kingdom, OX3 7G
Public contact	Clinical Trials and Research Governance, University of Oxford, ctrg@admin.ox.ac.uk
Scientific contact	Clinical Trials and Research Governance, University of Oxford, ctrg@admin.ox.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	12 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2018
Global end of trial reached?	Yes
Global end of trial date	12 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Principal research question:
Is a single dose of antibiotic following operative vaginal delivery clinically effective for preventing confirmed or presumed maternal infection?

Principal research objective:
To compare the incidence of confirmed or suspected maternal infection in the first six weeks after operative vaginal delivery amongst women who have received an antibiotic versus those who received placebo.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 2016
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: 3420
Worldwide total number of subjects	3420
EEA total number of subjects	3420

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)	23
Adults (18-64 years)	3397

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

March 13 2016 to June 13 2018 in 27 hospital obstetric units in the UK

Pre-assignment

Screening details:

No screening was conducted

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, Data analyst, Carer, Assessor

Blinding implementation details:

Women, most clinicians including research midwives and those taking consent, and all those collecting outcome information were blinded to allocation. Clinical staff responsible for preparing and checking the trial drug were not blinded to allocation but they played no other role in the trial. The Trial Statisticians and the DMC were blinded to trial allocation until the database was locked for the final analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Amoxicillin

Arm description:

Women in the intervention group received a single dose of intravenous amoxicillin/clavulanic acid (1g amoxicillin/200mg clavulanic acid) as soon as possible, and no more than six hours, after giving birth.

Arm type	Experimental
Investigational medicinal product name	Amoxicillan and clavulanic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g amoxicillan and 200mg clavulanic acid as soon as possible post-delivery and no more than 6 hours after giving birth

Arm title	Placebo

Arm description:

Women in the placebo group received 20ml of intravenous sterile 0.9% saline within six hours after giving birth.

Arm type	Placebo
Investigational medicinal product name	Sterile saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

20ml of intravenous sterile 0.9% saline as soon as possible post-delivery and no more than 6 hours after giving birth

Number of subjects in period 1	Amoxicillin	Placebo
Started	1715	1705
Completed	1715	1705

Baseline characteristics

Reporting groups	
Reporting group title	Amoxicillin
Reporting group description:	
Women in the intervention group received a single dose of intravenous amoxicillin/clavulanic acid (1g amoxicillin/200mg clavulanic acid) as soon as possible, and no more than six hours, after giving birth.	
Reporting group title	Placebo
Reporting group description:	
Women in the placebo group received 20ml of intravenous sterile 0.9% saline within six hours after giving birth.	

Reporting group values	Amoxicillin	Placebo	Total
Number of subjects	1715	1705	3420
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			
Maternal age at randomisation			
Units: years			
arithmetic mean	30.3	30.2	
standard deviation	± 5.37	± 5.49	-
Gender categorical Units: Subjects			
Female	1715	1705	3420
Male	0	0	0
Gestational age at randomisation Units: Subjects			
36 to <38	136	123	259
38 to <40	568	555	1123
40 to <42	964	968	1932
>=42	46	59	105
Not recorded	1	0	1
Ethnicity Units: Subjects			
White	1436	1474	2910
Indian	36	34	70
Pakistani	73	54	127
Bangladeshi	8	14	22
Black Caribbean	6	8	14

Black African	32	29	61
Other	116	85	201
Not recorded	8	7	15
Body mass index at booking kg/m2 Units: Subjects			
<18.5	46	48	94
18.5 to 24.9	851	842	1693
25 to 29.9	460	446	906
30 to 34.9	207	216	423
35 to 39.9	74	77	151
>=40	32	34	66
Not recorded	45	42	87
Twin pregnancy Units: Subjects			
Yes	11	9	20
Not recorded	0	0	0
No	1704	1696	3400
Any previous pregnancies>=22 weeks gestation Units: Subjects			
Yes	402	373	775
Not recorded	1	3	4
No	1312	1329	2641
Previous caesarean section Units: Subjects			
Yes	137	123	260
Missing	2	3	5
No	1576	1579	3155
Previous episiotomy Units: Subjects			
Yes	147	141	288
Not recorded	26	25	51
No	1542	1539	3081
Previous tear Units: Subjects			
Yes	81	80	161
No	1610	1599	3209
Not recorded	24	26	50
Rupture of membranes before delivery, hours Units: Subjects			
Yes	1692	1683	3375
Not recorded	0	0	0
No	23	22	45
Labour induction Units: Subjects			
Yes	819	852	1671
Not recorded	0	0	0
No	896	853	1749
Sequential instruments used Units: Subjects			
Yes	77	78	155

Missing	0	0	0
No	1638	1627	3265
Episiotomy in current delivery Units: Subjects			
Yes	1519	1525	3044
Not recorded	0	0	0
No	196	180	376
Perineal tear in current delivery Units: Subjects			
Yes	493	560	1053
Not recorded	0	0	0
No	1222	1145	2367
Perineal wound sutured Units: Subjects			
Yes	1645	1665	3310
Not recorded	54	33	87
No	16	7	23
Location of suturing Units: Subjects			
Operating theatre	571	588	1159
Delivery ward or room	1074	1076	2150
Not recorded	70	41	111

End points

End points reporting groups

Reporting group title	Amoxicillin
Reporting group description:	
Women in the intervention group received a single dose of intravenous amoxicillin/clavulanic acid (1g amoxicillin/200mg clavulanic acid) as soon as possible, and no more than six hours, after giving birth.	
Reporting group title	Placebo
Reporting group description:	
Women in the placebo group received 20ml of intravenous sterile 0.9% saline within six hours after giving birth.	

Primary: Confirmed or suspected maternal infection

End point title	Confirmed or suspected maternal infection
End point description:	
End point type	Primary
End point timeframe:	
6 weeks post-delivery	

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1715	1705		
Units: subjects				
Yes	180	306		
Not recorded	96	99		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Placebo v Amoxicillin
Number of subjects included in analysis	3420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.69

Secondary: Confirmed systemic infection on culture

End point title	Confirmed systemic infection on culture

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1715	1705		
Units: subjects				
Yes	11	25		
Not recorded	1	1		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	3420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.89

Secondary: Endometritus

End point title	Endometritus

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1715	1705		
Units: subjects				
Yes	15	23		
Not recorded	1	1		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	3420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.186
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.24

Secondary: New prescription of antibiotics with relevant indication

End point title	New prescription of antibiotics with relevant indication
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks post-delivery	

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1715	1705		
Units: subjects				
Yes	180	306		
Not recorded	96	99		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	3420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.69

Secondary: Superficial perineal wound incisional infection

End point title	Superficial perineal wound incisional infection
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks post-delivery	

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1715	1705		
Units: subject				
Yes	75	141		
Unrecorded	3	9		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo

Number of subjects included in analysis	3420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.53
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.37
upper limit	0.75

Secondary: Deep perineal wound incisional infection

End point title	Deep perineal wound incisional infection
End point description:	

End point type	Secondary
End point timeframe:	
6 weeks post-delivery	

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1715	1705		
Units: subject				
Yes	36	77		
Not recorded	5	11		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	3420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.46

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.28
upper limit	0.77

Secondary: Organ or space perineal wound incisional infection

End point title	Organ or space perineal wound incisional infection
End point description:	

End point type	Secondary
End point timeframe:	
6 weeks post-delivery	

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1715	1705		
Units: subject				
Yes	0	4		
Not recorded	7	11		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	3420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Sysetmatic sepsis according to modified SIRS criteria for pregnancy

End point title	Sysetmatic sepsis according to modified SIRS criteria for pregnancy

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1715	1705		
Units: subjects				
Yes	6	10		
Not recorded	9	16		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	3420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.59
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.16
upper limit	2.24

Secondary: Perineal pain

End point title	Perineal pain

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subjects				
Yes	592	707		
Not recorded	0	0		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.84
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.76
upper limit	0.93

Secondary: Use of pain relief for perineal pain

End point title	Use of pain relief for perineal pain

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subjects				
Yes	99	138		
Not recorded	13	18		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.72
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.52
upper limit	0.99

Secondary: Need for additional perineal care

End point title	Need for additional perineal care
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks post-delivery	

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subject				
Yes	390	543		
Not recorded	42	38		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.72

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.63
upper limit	0.83

Secondary: Wound breakdown

End point title	Wound breakdown

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subjects				
Yes	142	272		
Not recorded	4	7		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.52
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.41
upper limit	0.67

Secondary: Dyspareunia

End point title	Dyspareunia

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subjects				
Yes	299	280		
Not recorded	5	8		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.873
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.01
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.87
upper limit	1.17

Secondary: Breastfeeding at 6 weeks

End point title	Breastfeeding at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subjects				
Yes	662	657		
Not recorded	4	4		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.828
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.01
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.91
upper limit	1.11

Secondary: Perineum ever too painful or uncomfortable to feed baby

End point title	Perineum ever too painful or uncomfortable to feed baby

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subject				
Yes	136	198		
Not recorded	96	98		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00025
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.69
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.53
upper limit	0.9

Secondary: Hospital bed stay to discharge	
End point title	Hospital bed stay to discharge
End point description:	
End point type	Secondary
End point timeframe:	
To hospital discharge	

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: days				
median (inter-quartile range (Q1-Q3))	1 (1 to 2)	1 (1 to 2)		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.318
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Any primary care or home visits in relation to perineum

End point title	Any primary care or home visits in relation to perineum

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subjects				
Yes	361	496		
Not recorded	3	5		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.73
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.63
upper limit	0.84

Secondary: Any outpatient visits in relation to perineum

End point title	Any outpatient visits in relation to perineum

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subjects				
Yes	95	173		
Not recorded	5	6		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.55
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.4
upper limit	0.75

Secondary: Maternal hospital re-admission

End point title	Maternal hospital re-admission

End point description:

End point type	Secondary

End point timeframe:

6 weeks post-delivery

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: subjects				
Yes	63	84		
Not recorded	47	51		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.75
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.49
upper limit	1.14

Secondary: Maternal health-related quality of life at 6 weeks

End point title	Maternal health-related quality of life at 6 weeks
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks post-delivery	

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1296	1297		
Units: EQ-5D-5L score				
arithmetic mean (standard deviation)	0.935 (± 0.098)	0.927 (± 0.111)		

Statistical analyses

Statistical analysis title	Main comparison
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	2593
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.008
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.003
upper limit	0.019

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Time of administration of intervention to 6 hours post administration or hospital discharge - whichever was soon

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Amoxicillin

Reporting group description:

Women in the intervention group received a single dose of intravenous amoxicillin/clavulanic acid (1g amoxicillin/200mg clavulanic acid) as soon as possible, and no more than six hours, after giving birth.

Reporting group title	Placebo

Reporting group description:

Women in the placebo group received 20ml of intravenous sterile 0.9% saline within six hours after giving birth.

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: Non-serious adverse events were not routinely recorded as the IMP is a licensed product which is being given at a standard dose. However adverse events which are part of the study outcomes will be recorded in the CRF.

Serious adverse events	Amoxicillin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1715 (0.06%)	2 / 1705 (0.12%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Allergic reaction - Itching and swollen throat			
subjects affected / exposed	1 / 1715 (0.06%)	0 / 1705 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
post-partum haemorrhage	Additional description: Post-partum haemorrhage with blood transfusion		
subjects affected / exposed	0 / 1715 (0.00%)	1 / 1705 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
sepsis	Additional description: Woman admitted to ICU 15 days post natal with severe sepsis		

subjects affected / exposed	0 / 1715 (0.00%)	1 / 1705 (0.06%)	
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	Amoxicillin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1715 (0.00%)	0 / 1705 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2016	The following changes have been made to create Protocol Version 3.0 3rd December 2015: 8.3. Exclusion Criteria (page 16) In the point 'Note that receiving antenatal or postnatal antibiotics e.g. for maternal Group B Streptococcal carriage or prolonged rupture of membranes, is not a reason for exclusion if there is no indication for ongoing antibiotic prescription post-delivery.' the words 'or postnatal' have been removed because this wording was incorrect and contradicts the previous sentence. Reporting Serious Adverse Events (SAEs) and Procedure for immediate reporting of Serious Adverse Events (pages 25-26): Wording amended improve consistency and to make it clear that events which commence prior to the administration of the trial Intervention do not require reporting as an SAE. 9.5. Randomisation, blinding and code-breaking (pages 20) Text edited regarding balance and unpredictability from 'within centre' to 'overall' by Trial Statistician. Text edited to show that an emergency code-breaking procedure will not be required; as only a single dose of co-amoxiclav will be administered there is no need to code-break if further antibiotics are required. If a woman was to have an anaphylactic reaction she would be treated as if she has been given the active drug. Other edits to the Protocol in Version 3.0 are listed below: 1. The list of Investigators has been removed from the cover page to make the Protocol clearer and to ensure that the ANODE Trial team at the Clinical Trials Unit are approached with any Protocol queries in the first instance rather than a Co-investigator. The Investigators will be listed on the ANODE website. 2. The confidentiality statement has been removed from page 2 as the Protocol is no longer confidential and is available publicly.

22 April 2016	The following changes have been made to create Protocol Version 4.0 22nd April 2016: Section 7.0 Trial Design (page 15) Edits to this section have been made to specify exactly who will not be blinded to allocation to clarify that this also includes the person responsible for checking the intervention. The people not blinded to intervention will be the person who prepared the trial intervention and the person who checks the intervention prior to administration. Training will be provided to all unblinded staff on the importance of maintaining blinding and unblinded staff will not be involved in the collection of outcomes information. Other edits to the ANODE Protocol - Page 1 - ISRCTN added and signature blocks for the Chief Investigator and the Statistician have been removed; they will be documented separately and filed with the Protocol in the Trial Master File. - Global edit - where Hospital Episode Statistics (HES) is referenced 'or NHS Wales Informatics Service' has been added. HES will be accessed for participants recruited in England; NHS Wales Informatics Service will be accessed for those participants recruited in Wales. - Pages 15-16 and Appendix A - duration of study edited to reflect the change in start date agreed with the HTA. - Page 19 - edited to clarify that the original signed consent forms will be sent the coordinating centre and a copy retained at site. - Page 20 - section 9.5 edited to clarify the roles of the Senior Trials Statistician and the Senior Trial Programmer with regard to their responsibilities regarding the randomisation schedule generation.
30 November 2017	The following changes have been made to create Protocol Version 5.0 30th November 2017: Amendment to the definition of the primary outcome (pages 7, 9 (in flowchart), 14 and 20) Primary outcome refined to the amended text below: • A new prescription of antibiotics for presumed perineal wound-related infection, endometritis or uterine infection, urinary tract infection with systemic features or other systemic infection • Confirmed systemic infection on culture • Endometritis as defined by the US Centers for Disease Control and Prevention (Centers for Disease Control and Prevention 2013) Trial timeline updated to reflected changes following an extension to the duration of the trial (page 16 and page 39) 12.2 Description of Statistical Methods (page 27) The statistics section of the protocol has been updated to make it consistent with the current strategy detailed in the statistical analysis plan as requested by the ANODE Data Monitoring Committee in a meeting held on the the 27th November 2017.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported