Clinical trial results:
A Randomised Placebo Controlled Trial of the effectiveness of Early MEtformin in Addition to Usual Care in the Reduction of Gestational Diabetes Mellitus Effects (EMERGE)

Summary

EudraCT number	2016-001644-19
Trial protocol	IE
Global end of trial date	13 April 2023

Results information

Result version number	v1 (current)
This version publication date	28 April 2024
First version publication date	28 April 2024

Trial information

Trial identification

Sponsor protocol code	NUIG-2016-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HRB Clinical Research Facility Galway
Sponsor organisation address	University Road, Galway, Ireland,
Public contact	Fidelma Dunne , HRB Clinical Research Facility Galway, fidelma.dunne@nuigalway.ie
Scientific contact	Fidelma Dunne, HRB Clinical Research Facility Galway, fidelma.dunne@nuigalway.ie

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	10 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 April 2023
Global end of trial reached?	Yes
Global end of trial date	13 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine if metformin (a) reduces the requirement for insulin or (b) reduces fasting glucose at gestational weeks 32 and 38.

Protection of trial subjects:

The EMERGE trial was initially approved by Galway University Hospital Clinical Research Ethics Committee on 16th Dec 2016. The trial was transitioned to the National Research Ethics Committee (NREC-CT), following a substantial amendment to the protocol, in July 2021.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices (GCPs) and the applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2017
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	Ireland: 535
Worldwide total number of subjects	535
EEA total number of subjects	535

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)	535

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The population for the trial was pregnant women between the ages of 18-50 years, with a diagnosis of gestational diabetes mellitus (GDM) up to 28 weeks gestation.
Women were diagnosed with GDM using a 75g oral glucose tolerance test (OGTT).

Pre-assignment

Screening details:

2308 pregnancies were identified with gestational diabetes mellitus. 173 were excluded from participation- 1773 were outside the study window; 400 patients declined participation; 200 had partner that disagreed study participation; 50 already on study drug; 20 excluded per exclusion criteria; 5 had twin pregnancy; 2 known congenital anomalies.

Period 1

Period 1 title	Baseline
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:

Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study/during the active treatment phase of the study. Unblinding did not occur until the reporting database was validated and locked for final statistical analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin group

Arm description:

Women randomised to the Metformin Group received metformin 500mg OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of 2500mg Metformin daily (5 tablets) or maximum tolerated dose, in addition to usual care (exercise and MNT), and taken until delivery.

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

Dosage and administration details:

500mg OD by mouth, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of 2500mg Metformin daily (5 tablets) or maximum tolerated dose.

Arm title	Placebo

Arm description:

Subjects randomised to the Placebo Group received 1 placebo tablet OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of five placebo tablets daily, in addition to usual care (exercise and MNT), and taken until delivery.

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:

1 placebo tablet OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of five placebo tablets daily.

Number of subjects in period 1	Metformin group	Placebo
Started	268	267
Completed	268	267

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

Arms	
Are arms mutually exclusive?	Yes
Arm title	Metformin

Arm description: -

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

Dosage and administration details:

500mg OD by mouth, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of 2500mg Metformin daily (5 tablets) or maximum tolerated dose.

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

Dosage and administration details:

Subjects randomised to the Placebo Group received 1 placebo tablet OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of five placebo tablets daily, in addition to usual care (exercise and MNT), and taken until delivery.

Arm title	Placebo

Arm description: -	
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:

1 placebo tablet OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of five placebo tablets daily.

Number of subjects in period 2	Metformin	Placebo
Started	268	267
Completed	263	265
Not completed	5	2
Consent withdrawn by subject	4	1
Other	1	1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	oMetformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg OD by mouth, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of 2500mg Metformin daily (5 tablets) or maximum tolerated dose.

Arm title	Placebo

Arm description: -	
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:

1 placebo tablet OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of five placebo tablets daily.

Number of subjects in period 3	Metformin	Placebo
Started	263	265
Completed	211	220
Not completed	52	45
Adverse event, serious fatal	1	-
Consent withdrawn by subject	3	4
Physician decision	-	1
Other	30	22
Lost to follow-up	18	18

Baseline characteristics

Reporting groups	
Reporting group title	Metformin group
Reporting group description:	
Women randomised to the Metformin Group received metformin 500mg OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of 2500mg Metformin daily (5 tablets) or maximum tolerated dose, in addition to usual care (exercise and MNT), and taken until delivery.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised to the Placebo Group received 1 placebo tablet OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of five placebo tablets daily, in addition to usual care (exercise and MNT), and taken until delivery.	

Reporting group values	Metformin group	Placebo	Total
Number of subjects	268	267	535
Age categorical			
Age in years at baseline			
Units: Subjects			
Adults (18-64 years)	268	267	535
Age continuous			
Age (years)			
Units: years			
arithmetic mean	34.3	34.3	
standard deviation	± 4.9	± 4.7	-
Gender categorical			
Gender			
Units: Subjects			
Female	268	267	535
Male	0	0	0
Race/Ethnic Group Units: Subjects			
African	6	6	12
Asian, other	17	29	46
Irish	175	171	346
Irish Traveller	11	2	13
Other	14	21	35
White, other	44	38	82
Black, other	1	0	1
Not recorded	0	0	0
Educational Level			
Level of education completed			
Units: Subjects			
Primary only	25	12	37
Secondary only	78	78	156
Tertiary education	165	176	341
Not recorded		1	1
Employment status Units: Subjects			
Unemployed	19	27	46

Other	249	239	488
Not recorded		1	1
Have a medical card Units: Subjects			
Yes	63	63	126
No	205	203	408
Not recorded		1	1
Have Private Health Insurance Units: Subjects			
Yes	126	116	242
No	142	150	292
Not recorded		1	1
Smoking Status Units: Subjects			
Current	17	17	34
Former	124	100	224
Never	127	150	277
Not recorded	0	0	0
Nulliparous Units: Subjects			
Yes	84	84	168
No	184	183	367
Not recorded	0	0	0
History of Macrosomia			
Prior delivery of infant with birthweight >4000g			
Units: Subjects			
Yes	57	44	101
No	211	223	434
Not recorded	0	0	0
History of Miscarriage Units: Subjects			
Yes	106	93	199
No	162	174	336
NA	0	0	0
Not recorded	0	0	0
History of Congenital Deformities			
Prior pregnancy with delivery of infant with congenital deformities.			
Units: Subjects			
Yes	13	13	26
No	255	254	509
NA	0	0	0
Not recorded	0	0	0
History of Gestational Diabetes Units: Subjects			
Yes	64	64	128
No	120	119	239
NA	84	84	168
Not recorded	0	0	0
History of Pre-eclampsia Units: Subjects			
Yes	24	23	47

No	160	160	320
NA	84	84	168
Not recorded	0	0	0
History of Postpartum Haemorrhage Units: Subjects			
Yes	28	20	48
No	156	163	319
NA	84	84	168
Not recorded	0	0	0
History of Polyhydramnios Units: Subjects			
Yes	10	7	17
No	258	260	518
Not recorded	0	0	0
History of Antepartum Haemorrhage Units: Subjects			
Yes	20	15	35
No	164	168	332
NA	84	84	168
Not recorded	0	0	0
History of Stillbirth Units: Subjects			
Yes	2	2	4
No	182	181	363
NA	84	84	168
Not recorded	0	0	0
Body Mass Index			
BMI kg/m2			
Units: kg/m2			
arithmetic mean	30.4	30.7	
standard deviation	± 6.4	± 5.7	-
Systolic blood pressure Units: mmHg			
arithmetic mean	114.9	114.4	
standard deviation	± 9.5	± 9.2	-
Diastolic blood pressure Units: mmHg			
arithmetic mean	68.9	68.7	
standard deviation	± 8.0	± 8.8	-
HbA1c Units: mmol/mol			
arithmetic mean	33.0	32.9	
standard deviation	± 3.4	± 3.5	-
Fasting serum glucose			
Overnight fasting serum glucose			
Units: mmol/l			
arithmetic mean	5.2	5.2	
standard deviation	± 0.5	± 0.5	-
1 hour glucose tolerance test result Units: mmol/l			
arithmetic mean	9.4	9.7	

standard deviation	± 1.9	± 1.9	-
2 hours glucose tolerance test value Units: mmol/l			
arithmetic mean	7.1	7.1	
standard deviation	± 1.6	± 1.6	-

Subject analysis sets	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:
The intention to treat (ITT) analysis set will include all randomised subjects.

Reporting group values	Intention to treat		
Number of subjects	535		
Age categorical			
Age in years at baseline			
Units: Subjects			
Adults (18-64 years)	268		
Age continuous			
Age (years)			
Units: years			
arithmetic mean	34.3		
standard deviation	± 4.8		
Gender categorical			
Gender			
Units: Subjects			
Female	535		
Male	0		
Race/Ethnic Group Units: Subjects			
African	12		
Asian, other	46		
Irish	346		
Irish Traveller	13		
Other	35		
White, other	82		
Black, other	1		
Not recorded	0		
Educational Level			
Level of education completed			
Units: Subjects			
Primary only	37		
Secondary only	156		
Tertiary education	341		
Not recorded	1		
Employment status Units: Subjects			
Unemployed	46		
Other	488		
Not recorded	1		

Have a medical card Units: Subjects			
Yes	126		
No	408		
Not recorded	1		
Have Private Health Insurance Units: Subjects			
Yes	242		
No	292		
Not recorded	1		
Smoking Status Units: Subjects			
Current	34		
Former	224		
Never	277		
Not recorded	0		
Nulliparous Units: Subjects			
Yes	168		
No	367		
Not recorded	0		
History of Macrosomia			
Prior delivery of infant with birthweight >4000g			
Units: Subjects			
Yes	101		
No	434		
Not recorded	0		
History of Miscarriage Units: Subjects			
Yes	199		
No	336		
NA	0		
Not recorded	0		
History of Congenital Deformities			
Prior pregnancy with delivery of infant with congenital deformities.			
Units: Subjects			
Yes	26		
No	509		
NA	0		
Not recorded	0		
History of Gestational Diabetes Units: Subjects			
Yes	128		
No	239		
NA	168		
Not recorded	0		
History of Pre-eclampsia Units: Subjects			
Yes	47		
No	320		
NA	168		

Not recorded	0		
History of Postpartum Haemorrhage Units: Subjects			
Yes	48		
No	319		
NA	168		
Not recorded	0		
History of Polyhydramnios Units: Subjects			
Yes	17		
No	434		
Not recorded	0		
History of Antepartum Haemorrhage Units: Subjects			
Yes	35		
No	332		
NA	168		
Not recorded	0		
History of Stillbirth Units: Subjects			
Yes	4		
No	363		
NA	168		
Not recorded	0		
Body Mass Index			
BMI kg/m2			
Units: kg/m2			
arithmetic mean	30.5		
standard deviation	± 6.1		
Systolic blood pressure Units: mmHg			
arithmetic mean	114.6		
standard deviation	± 9.4		
Diastolic blood pressure Units: mmHg			
arithmetic mean	68.8		
standard deviation	± 8.4		
HbA1c Units: mmol/mol			
arithmetic mean	32.9		
standard deviation	± 3.5		
Fasting serum glucose			
Overnight fasting serum glucose			
Units: mmol/l			
arithmetic mean	5.2		
standard deviation	± 0.5		
1 hour glucose tolerance test result Units: mmol/l			
arithmetic mean	9.5		
standard deviation	± 1.9		
2 hours glucose tolerance test value			

Units: mmol/l			
arithmetic mean	7.1		
standard deviation	± 1.6		

End points

End points reporting groups

Reporting group title	Metformin group
Reporting group description:	
Women randomised to the Metformin Group received metformin 500mg OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of 2500mg Metformin daily (5 tablets) or maximum tolerated dose, in addition to usual care (exercise and MNT), and taken until delivery.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised to the Placebo Group received 1 placebo tablet OD, with the dose titrated upwards every 2 days over 10 days increasing to a maximum of five placebo tablets daily, in addition to usual care (exercise and MNT), and taken until delivery.	
Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention to treat (ITT) analysis set will include all randomised subjects.	

Primary: Insulin Initiated Yes/No

End point title	Insulin Initiated Yes/No
End point description:	
End point type	Primary
End point timeframe:	
Initiation of insulin treatment at any time prior to delivery.	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Yes	101	134	235	
No	167	133	300	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Biinary logistic regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.005
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.86

Notes:

[1] - Two-sided

Primary: Composite outcome	
End point title	Composite outcome
End point description:	
Initiation of insulin OR fasting glucose at 32 weeks' gestation >=5.1mmol/l OR fasting glucose at 38 weeks' gestation >=5.1mmol/l	
End point type	Primary
End point timeframe:	
Any time prior to delivery.	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Yes	150	167	317	
No	118	100	218	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.1
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.06

Notes:
[2] - Two-sided

Primary: Fasting hyperglycaemia

End point title	Fasting hyperglycaemia

End point description:

End point type	Primary

End point timeframe:
Overall trial

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: Subjects				
Yes	94	106	200	
No	174	161	335	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.005
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.12

Notes:
[3] - Two-sided

Secondary: Pre-eclampsia

End point title	Pre-eclampsia
End point description:	
Subject diagnosed with pre-eclampsia.	
End point type	Secondary
End point timeframe:	
Any time during pregnancy	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Yes	9	5	14	
No	259	261	520	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.282
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	6.04

Notes:
[4] - Two-sided

Secondary: Pregnancy-induced hypertension	
End point title	Pregnancy-induced hypertension
End point description:	
Diagnosed with. Pregnancy-induced hypertension at any time during pregnancy	
End point type	Secondary
End point timeframe:	
Any time during pregnancy	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Yes	17	19	36	
No	251	248	499	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.739
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.76

Notes:
[5] - Two-sided

Secondary: Labour type

End point title	Labour type
End point description:	
Whether labour spontaneous or induced or delivery by elective Caesarian Section	
End point type	Secondary
End point timeframe:	
Labour	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Induced	73	87	160	
Elective Caesarian Section	116	101	217	
Spontaneous	70	74	114	

Statistical analyses

Statistical analysis title	Multinomial Logistic Regression
Statistical analysis description: Caesarean delivery	
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.367
Method	Multinomial Logistic Regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.85

Notes:
[6] - Two-sided

Statistical analysis title	Multinomial Logistic Regression
Statistical analysis description: Induced delivery	
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.603
Method	Multinomial Logistic Regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.39

Notes:
[7] - Two-sided

Secondary: Weight Gain during pregnancy

End point title	Weight Gain during pregnancy

End point description:

End point type	Secondary

End point timeframe:

Difference between weight at baseline and weight prior to delivery

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: kg				
arithmetic mean (standard deviation)	0.9 (± 3.3)	2 (± 3.5)	1.4 (± 3.5)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo v Intention to treat
Number of subjects included in analysis	1070
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.005
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.84
upper limit	-0.32

Notes:

[8] - Two-sided

Secondary: Postpartum impaired fasting glucose

End point title	Postpartum impaired fasting glucose

End point description:

Impaired fasting glucose was diagnosed if fasting glucose level was 5.6-6.9 mm/L .

End point type	Secondary

End point timeframe:

12 weeks postpartum

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Yes	51	52	103	
No	217	215	432	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.99
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.55

Notes:

[9] - Two-sided

Secondary: Postpartum impaired glucose tolerance by 2hr OGTT

End point title	Postpartum impaired glucose tolerance by 2hr OGTT

End point description:

Impaired glucose tolerance was diagnosed when 2hr OGTT result was 7.8-11 mmol/L.

End point type	Secondary

End point timeframe:

12 weeks postpartum

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Yes	15	16	31	
No	253	251	504	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.911
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	2

Notes:

[10] - Two-sided

Secondary: Postpartum metabolic syndrome

End point title	Postpartum metabolic syndrome

End point description:

Metabolic Syndrome was diagnosed if the participant had three or more of the following: (a) abdominal obesity with waist circumference >88cm (b) hypertriglyceridaemia >1.69mmol/l (c) low HDL < 1.29mmol/l (d) high blood pressure >130/85 mmHg (e) fasting glucose >6.1mmol/l.

End point type	Secondary

End point timeframe:

12 weeks postpartum

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Yes	20	25	45	
No	248	242	490	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.519
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.51

Notes:
[11] - Two-sided

Secondary: Birth weight	
End point title	Birth weight
End point description: Infant birth weight	
End point type	Secondary
End point timeframe: Birth	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: g				
arithmetic mean (standard deviation)	3393.5 (± 527.2)	3504.8 (± 509.7)	3449.2 (± 521.0)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo v Intention to treat
Number of subjects included in analysis	1070
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.014
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-111.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-200.28
upper limit	-22.46

Notes:
[12] - Two-sided

Secondary: Large for gestational age

End point title	Large for gestational age

End point description:

End point type	Secondary

End point timeframe:
At birth

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: neonates				
Yes	17	39	56	
No	251	228	479	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.71

Notes:
[13] - Two-sided

Secondary: Small for gestational age

End point title	Small for gestational age
End point description:	

End point type	Secondary
End point timeframe:	
At birth	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: neonates				
Yes	15	7	22	
No	253	260	513	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.089
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	5.88

Notes:
[14] - Two-sided

Secondary: Antepartum hemorrhage

End point title	Antepartum hemorrhage
End point description:	
Diagnosed with antepartum hemorrhage any time during pregnancy	
End point type	Secondary
End point timeframe:	
Any time during pregnancy	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: subjects				
Yes	15	27	42	
No	253	240	493	
Not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.058
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.01

Notes:
[15] - Two-sided

Secondary: Infant crown-heel lenght

End point title	Infant crown-heel lenght

End point description:

End point type	Secondary

End point timeframe:
at birth

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: cm				
arithmetic mean (standard deviation)	51 (± 3.2)	51.7 (± 3.2)	51.3 (± 3.2)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo v Intention to treat
Number of subjects included in analysis	1070
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.62
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.25

Notes:
[16] - two-sided

Secondary: Need for neonatal ICU

End point title	Need for neonatal ICU

End point description:

End point type	Secondary

End point timeframe:
early neonatal period

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: neonates				
yes	41	33	74	
no	227	234	461	
not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo v Intention to treat

Number of subjects included in analysis	1070
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.308
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.13

Notes:
[17] - two-sided

Secondary: Respiratory distress syndrome

End point title	Respiratory distress syndrome

End point description:

End point type	Secondary

End point timeframe:
early neonatal period

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: neonates				
yes	24	18	42	
no	244	249	493	
not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.33
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.63

Notes:
[18] - two-sided

Secondary: Jaundice

End point title	Jaundice

End point description:

End point type	Secondary

End point timeframe:
early neonatal period

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: neonates				
yes	128	132	260	
no	140	135	275	
not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.76
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.33

Notes:
[19] - two-sided

Secondary: Major cogenital anomalies

End point title	Major cogenital anomalies

End point description:

End point type	Secondary

End point timeframe:

early neonatal period

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: neonates				
yes	10	7	17	
no	258	260	518	
not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.457
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	4.05

Notes:

[20] - two-sided

Secondary: APGAR score

End point title	APGAR score

End point description:

End point type	Secondary

End point timeframe:

5 minutes postpartum

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: number				
median (inter-quartile range (Q1-Q3))	9 (9 to 9)	9 (9 to 9)	9 (9 to 9)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.664
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.11

Notes:
[21] - two-sided

Secondary: Neonatal hypoglycaemia

End point title	Neonatal hypoglycaemia

End point description:

End point type	Secondary

End point timeframe:
early neonatal period

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: neonates				
yes	34	25	59	
no	234	242	476	
not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.21
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	2.48

Notes:
[22] - two-sided

Secondary: Infant morbidities	
End point title	Infant morbidities
End point description:	
End point type	Secondary
End point timeframe:	
early neonatal period	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: neonates				
yes	144	147	291	
no	124	120	244	
not recorded	0	0	0	

Statistical analyses

Statistical analysis title	Binary Logistic Regression
Comparison groups	Metformin v Placebo

Number of subjects included in analysis	535
Analysis specification	Post-hoc
Analysis type	other[23]
P-value	= 0.83
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.36

Notes:
[23] - two-sided

Secondary: DTSQ satisfaction scale

End point title	DTSQ satisfaction scale

End point description:

End point type	Secondary

End point timeframe:
Week 12 visit

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: score				
median (inter-quartile range (Q1-Q3))	34 (31 to 36)	33 (29 to 36)	34 (30 to 36)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.288
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.35

Notes:
[24] - Two-sided

Secondary: DTSQ burden scale

End point title	DTSQ burden scale

End point description:

End point type	Secondary

End point timeframe:
Week 12 visit

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: score				
median (inter-quartile range (Q1-Q3))	2 (1 to 3)	2 (1 to 4)	2 (1 to 4)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.003
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	-0.24

Notes:
[25] - Two-sided

Secondary: Gestational age at birth

End point title	Gestational age at birth

End point description:

End point type	Secondary

End point timeframe:
At birth

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: weeks				
median (inter-quartile range (Q1-Q3))	39.4 (38.6 to 40.0)	39.3 (38.7 to 40.0)	39.3 (38.7 to 40.0)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.662
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.19

Notes:
[26] - Two-sided

Secondary: Maternal BMI

End point title	Maternal BMI

End point description:

End point type	Secondary

End point timeframe:
12 weeks post partum

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: kg/m^2				
median (inter-quartile range (Q1-Q3))	28.2 (25.2 to 32.1)	29.7 (26.6 to 34.5)	29.1 (25.8 to 33.2)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.018
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	-0.21

Notes:
[27] - Two-sided

Secondary: Maternal waist circumference	
End point title	Maternal waist circumference
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks postpartum	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: cm				
arithmetic mean (standard deviation)	93 (± 13)	95.2 (± 12.2)	94.0 (± 12.6)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Metformin v Placebo

Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.061
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.51
upper limit	0.1

Secondary: Infant head circumference

End point title	Infant head circumference
End point description:	

End point type	Secondary
End point timeframe:	
at birth	

End point values	Metformin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	268	267	535	
Units: cm				
arithmetic mean (standard deviation)	34.7 (± 1.6)	34.7 (± 1.8)	34.7 (± 1.7)	

Statistical analyses

Statistical analysis title	Linear Regression
Comparison groups	Placebo v Metformin
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.762
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.25

Notes:
[28] - Two-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Maternal events during pregnancy and up to 12 weeks postpartum; Neonatal events intrapartum and early neonatal period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Metformin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	159 / 262 (60.69%)	172 / 263 (65.40%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	2	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma	Additional description: Haemangioma		
subjects affected / exposed	3 / 262 (1.15%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma to right neck	Additional description: Haemangioma to right neck		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangiomas	Additional description: Haemangiomas		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemangiomas	Additional description: Hemangiomas		

subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Naevus	Additional description: Naevus		
subjects affected / exposed	0 / 262 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nevus simplex	Additional description: Nevus simplex		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Exacerbation of essential hypertension	Additional description: Exacerbation of essential hypertension		
subjects affected / exposed	2 / 262 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haematoma	Additional description: Subgaleal haematoma		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial thrombophlebitis	Additional description: Superficial thrombophlebitis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Monitoring post vaccine	Additional description: Monitoring post vaccine		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presumed early onset sepsis from gbs infection	Additional description: Presumed early onset sepsis from gbs infection		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prophylactic antibiotic administration	Additional description: Prophylactic antibiotic administration		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected sepsis	Additional description: Suspected sepsis		
subjects affected / exposed	1 / 262 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Absent end diastolic flow umbilical artery	Additional description: Absent end diastolic flow umbilical artery		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal tightenings	Additional description: Abdominal tightenings		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Birth weight less than 2500g	Additional description: Birth weight less than 2500g		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breastfeeding jaundice	Additional description: Breastfeeding jaundice		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestatic jaundice	Additional description: Cholestatic jaundice		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cephalohaematoma	Additional description: Cephalohaematoma		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contractions	Additional description: Contractions		
subjects affected / exposed	0 / 262 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Excessive weight loss after birth	Additional description: Excessive weight loss after birth		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fetal growth restriction	Additional description: Fetal growth restriction		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Growth restriction	Additional description: Growth restriction		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hellp syndrome	Additional description: Hellp syndrome		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Jaundice	Additional description: Jaundice		
subjects affected / exposed	3 / 262 (1.15%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Irritable uterus	Additional description: Irritable uterus		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intrauterine growth restriction (iugr)	Additional description: Intrauterine growth restriction (iugr)		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intra-uterine death at 34 weeks gestation	Additional description: Intra-uterine death at 34 weeks gestation

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intermittent absent end diastolic flow	Additional description: Intermittent absent end diastolic flow		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased head circumference measurement	Additional description: Increased head circumference measurement		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive disorder in pregnancy	Additional description: Hypertensive disorder in pregnancy		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low birthweight due to prematurity	Additional description: Low birthweight due to prematurity		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low birth weight	Additional description: Low birth weight		
subjects affected / exposed	2 / 262 (0.76%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal jaundice	Additional description: Neonatal jaundice		
subjects affected / exposed	2 / 262 (0.76%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nicu admission for low birth weight	Additional description: Nicu admission for low birth weight		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oligohydamnios	Additional description: Oligohydamnios		

subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oligohydramnios	Additional description: Oligohydramnios		
subjects affected / exposed	3 / 262 (1.15%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological (dct positive) jaundice	Additional description: Pathological (dct positive) jaundice		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persistant jaundice	Additional description: Persistant jaundice		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placental abruption	Additional description: Placental abruption		
subjects affected / exposed	1 / 262 (0.38%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyhydramnios	Additional description: Polyhydramnios		
subjects affected / exposed	0 / 262 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible intrauterine growth restriction	Additional description: Possible intrauterine growth restriction		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible pet	Additional description: Possible pet		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible placental abruption	Additional description: Possible placental abruption		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia	Additional description: Pre-eclampsia		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-term labour	Additional description: Pre-term labour		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prematurity	Additional description: Prematurity		
subjects affected / exposed	4 / 262 (1.53%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pressure with decreased foetal movement	Additional description: Pressure with decreased foetal movement		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-partum haemorrhage	Additional description: Post-partum haemorrhage		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Query pre-term labour	Additional description: Query pre-term labour		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced feeding/ weight loss >10% of birth weight	Additional description: Reduced feeding/ weight loss >10% of birth weight		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced fetal movement	Additional description: Reduced fetal movement		

subjects affected / exposed	8 / 262 (3.05%)	8 / 263 (3.04%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced fetal movements	Additional description: Reduced fetal movements		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced foetal movement	Additional description: Reduced foetal movement		
subjects affected / exposed	8 / 262 (3.05%)	7 / 263 (2.66%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retained placenta	Additional description: Retained placenta		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retained placental tissue	Additional description: Retained placental tissue		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary post partum haemorrhage	Additional description: Secondary post partum haemorrhage		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small for gestational age	Additional description: Small for gestational age		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected pre-term labour	Additional description: Suspected pre-term labour		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Threatened pre-term labour	Additional description: Threatened pre-term labour		

subjects affected / exposed	2 / 262 (0.76%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Threatened preterm labour	Additional description: Threatened preterm labour		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical cord prolapse	Additional description: Umbilical cord prolapse		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unstable fetal lie in utero	Additional description: Unstable fetal lie in utero		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unstable lie	Additional description: Unstable lie		
subjects affected / exposed	1 / 262 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss	Additional description: Weight loss		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss >10% of birth weight	Additional description: Weight loss >10% of birth weight		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss greater than 10%	Additional description: Weight loss greater than 10%		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss of more than 10% since birth	Additional description: Weight loss of more than 10% since birth		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss > 10% of birth weight	Additional description: Weight loss > 10% of birth weight		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain due to anemia	Additional description: Chest pain due to anemia		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	2 / 262 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeling weak	Additional description: Feeling weak		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left calf swelling	Additional description: Left calf swelling		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain and pressure upper chest	Additional description: Pain and pressure upper chest		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain post c-section and tubal ligation	Additional description: Pain post c-section and tubal ligation		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain under breast bone bilaterally	Additional description: Pain under breast bone bilaterally		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen lower left limb	Additional description: Swollen lower left limb		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen right leg	Additional description: Swollen right leg		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Post vaccine reaction	Additional description: Post vaccine reaction		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Patient thought her waters broke	Additional description: Patient thought her waters broke		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal bleed	Additional description: Vaginal bleed		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal discharge	Additional description: Vaginal discharge		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vaginal spotting	Additional description: Vaginal spotting		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis	Additional description: Cyanosis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Massive pulmonary embolism	Additional description: Massive pulmonary embolism		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Low oxygen saturation levels	Additional description: Low oxygen saturation levels		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary emboli	Additional description: Pulmonary emboli		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest	Additional description: Respiratory arrest		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory distress	Additional description: Respiratory distress		
subjects affected / exposed	7 / 262 (2.67%)	10 / 263 (3.80%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress syndrome	Additional description: Respiratory distress syndrome		
subjects affected / exposed	3 / 262 (1.15%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient tachypnea of the newborn	Additional description: Transient tachypnea of the newborn		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea	Additional description: Tachypnoea		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient tachypnoea of newborn	Additional description: Transient tachypnoea of newborn		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient tachypnoea of the newborn	Additional description: Transient tachypnoea of the newborn		
subjects affected / exposed	6 / 262 (2.29%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Irritability	Additional description: Irritability		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Borderline elevated blood pressure	Additional description: Borderline elevated blood pressure		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Deranged liver function tests	Additional description: Deranged liver function tests		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elevated blood pressure	Additional description: Elevated blood pressure		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart murmur	Additional description: Heart murmur		
subjects affected / exposed	2 / 262 (0.76%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raised blood pressure	Additional description: Raised blood pressure		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systolic murmur	Additional description: Systolic murmur		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss	Additional description: Weight loss		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture	Additional description: Ankle fracture		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Close contact with group a streptococus	Additional description: Close contact with group a streptococus		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contact in person with ringworm	Additional description: Contact in person with ringworm		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall	Additional description: Fall		
subjects affected / exposed	2 / 262 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip subluxation	Additional description: Hip subluxation		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematoma over caesarean section scar	Additional description: Haematoma over caesarean section scar		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Head injury	Additional description: Head injury		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache	Additional description: Headache		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Patient fell at home	Additional description: Patient fell at home		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reaction to 2 month vaccine	Additional description: Reaction to 2 month vaccine		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skull fracture	Additional description: Skull fracture

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal headache	Additional description: Spinal headache		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial burn to right hand	Additional description: Superficial burn to right hand		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected hip subluxation	Additional description: Suspected hip subluxation		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tick bite	Additional description: Tick bite		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trauma to right abdomen post fall	Additional description: Trauma to right abdomen post fall		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
?Tongue tie	Additional description: ?Tongue tie		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic arch hypoplasia	Additional description: Aortic arch hypoplasia		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial septal defect	Additional description: Atrial septal defect		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial septal defect (asd)	Additional description: Atrial septal defect (asd)		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bifid uvula	Additional description: Bifid uvula		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilateral cryptorchidism	Additional description: Bilateral cryptorchidism		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilateral hydroceles	Additional description: Bilateral hydroceles		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilateral webbed feet	Additional description: Bilateral webbed feet		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Birthmark	Additional description: Birthmark		
subjects affected / exposed	8 / 262 (3.05%)	8 / 263 (3.04%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Birthmark on nape of neck	Additional description: Birthmark on nape of neck		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Birthmarks	Additional description: Birthmarks		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cleft lip	Additional description: Cleft lip		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cleft gum	Additional description: Cleft gum		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chordee	Additional description: Chordee		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital dermal melanocytosis	Additional description: Congenital dermal melanocytosis		
subjects affected / exposed	6 / 262 (2.29%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital heart defect	Additional description: Congenital heart defect		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital heart defects (chd)	Additional description: Congenital heart defects (chd)		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital melanocytic naevus	Additional description: Congenital melanocytic naevus		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital pneumonia	Additional description: Congenital pneumonia		

subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal melanocytosis	Additional description: Dermal melanocytosis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptorchidism	Additional description: Cryptorchidism		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epispadias	Additional description: Epispadias		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left sided torticollis	Additional description: Left sided torticollis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocele	Additional description: Hydrocele		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngomalacia	Additional description: Laryngomalacia		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypospadias	Additional description: Hypospadias		
subjects affected / exposed	2 / 262 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mongolion blue spot	Additional description: Mongolion blue spot		

subjects affected / exposed	0 / 262 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mongolian blue spots	Additional description: Mongolian blue spots		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mongolian blue spot birthmark	Additional description: Mongolian blue spot birthmark		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mongolian blue spot	Additional description: Mongolian blue spot		
subjects affected / exposed	2 / 262 (0.76%)	7 / 263 (2.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip tie	Additional description: Lip tie		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple congenital dermal melanocytosis	Additional description: Multiple congenital dermal melanocytosis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Naevus simplex	Additional description: Naevus simplex		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nevus flammeus simplex	Additional description: Nevus flammeus simplex		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nevus simplex	Additional description: Nevus simplex		

subjects affected / exposed	0 / 262 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patent foramen ovale	Additional description: Patent foramen ovale		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persistent pulmonary hypertension of the newborn	Additional description: Persistent pulmonary hypertension of the newborn		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polydactyly	Additional description: Polydactyly		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible foetal hydronephrosis	Additional description: Possible foetal hydronephrosis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible hydrocele	Additional description: Possible hydrocele		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible hypospadias	Additional description: Possible hypospadias		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pectus carinatum	Additional description: Pectus carinatum		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Preauricular skin tag	Additional description: Preauricular skin tag		

subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric stenosis	Additional description: Pyloric stenosis		
subjects affected / exposed	2 / 262 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected laryngomalacia	Additional description: Suspected laryngomalacia		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmon patch right eyelid and nasal bridge	Additional description: Salmon patch right eyelid and nasal bridge		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin tag	Additional description: Skin tag		
subjects affected / exposed	1 / 262 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stork mark	Additional description: Stork mark		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected ventricular septal defect	Additional description: Suspected ventricular septal defect		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Talipes	Additional description: Talipes		
subjects affected / exposed	1 / 262 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Talipes varus	Additional description: Talipes varus		

subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue tie	Additional description: Tongue tie		
subjects affected / exposed	20 / 262 (7.63%)	35 / 263 (13.31%)	
occurrences causally related to treatment / all	0 / 20	0 / 35	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trisomy 13	Additional description: Trisomy 13		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Unilateral cryptorchidism	Additional description: Unilateral cryptorchidism		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Undescended right testicle	Additional description: Undescended right testicle		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trisomy 21	Additional description: Trisomy 21		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular septal defect	Additional description: Ventricular septal defect		
subjects affected / exposed	2 / 262 (0.76%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal bradycardia	Additional description: Fetal bradycardia		

subjects affected / exposed	0 / 262 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal bradycardia in labour	Additional description: Fetal bradycardia in labour		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal bradycardia	Additional description: Foetal bradycardia		
subjects affected / exposed	2 / 262 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maternal tachycardia	Additional description: Maternal tachycardia		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persistent maternal tachycardia	Additional description: Persistent maternal tachycardia		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Focal migraine	Additional description: Focal migraine		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grade 4 intraventricular haemorrhage	Additional description: Grade 4 intraventricular haemorrhage		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache		

subjects affected / exposed	2 / 262 (0.76%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine headache	Additional description: Migraine headache		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine aura	Additional description: Migraine aura		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital headache	Additional description: Occipital headache		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible bell's palsy	Additional description: Possible bell's palsy		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible evolving pet (pre-eclamptic toxaemia)	Additional description: Possible evolving pet (pre-eclamptic toxaemia)		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome	Additional description: Posterior reversible encephalopathy syndrome		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome (pres	Additional description: Posterior reversible encephalopathy syndrome (pres		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-syncope	Additional description: Pre-syncope		

subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seventh nerve palsy	Additional description: Seventh nerve palsy		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe frontal headache	Additional description: Severe frontal headache		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Syncope		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 262 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Echogenic mass on ultrasound	Additional description: Echogenic mass on ultrasound		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye twitching/jerking episode	Additional description: Eye twitching/jerking episode		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pale optic disc	Additional description: Pale optic disc		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ptosis	Additional description: Ptosis		

subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	4 / 262 (1.53%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal cramps	Additional description: Abdominal cramps		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Admitted with abdominal pain and contractions 1:10	Additional description: Admitted with abdominal pain and contractions 1:10		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Admitted with abdominal pain	Additional description: Admitted with abdominal pain		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colic	Additional description: Colic		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastro-intestinal upset	Additional description: Gastro-intestinal upset		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastro-oesophageal reflux	Additional description: Gastro-oesophageal reflux		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal upset	Additional description: Gastrointestinal upset		
subjects affected / exposed	5 / 262 (1.91%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left lower abdominal pain.	Additional description: Left lower abdominal pain.		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left sided abdominal pain	Additional description: Left sided abdominal pain		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower abdominal pain	Additional description: Lower abdominal pain		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left-sided abdominal pain	Additional description: Left-sided abdominal pain		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nipple confusion	Additional description: Nipple confusion		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Projectile vomiting	Additional description: Projectile vomiting		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small anal fissure	Additional description: Small anal fissure		

subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right sided inguinal hernia	Additional description: Right sided inguinal hernia		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper abdominal pain	Additional description: Upper abdominal pain		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral gastritis	Additional description: Viral gastritis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	2 / 262 (0.76%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis	Additional description: Cholestasis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis	Additional description: Cholecystitis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient neonatal hepatitis	Additional description: Transient neonatal hepatitis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Caesearen section scar tenderness	Additional description: Caesearen section scar tenderness		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Casarean section scar tenderness	Additional description: Casarean section scar tenderness		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised rash on all limbs and torso	Additional description: Generalised rash on all limbs and torso		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritic rash	Additional description: Pruritic rash		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uriticaria to chin	Additional description: Uriticaria to chin		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease 3a	Additional description: Chronic kidney disease 3a		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elevated protein creatinine level (pcr)	Additional description: Elevated protein creatinine level (pcr)		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ketonuria	Additional description: Ketonuria		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Moderate right hydronephrosis	Additional description: Moderate right hydronephrosis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meatal stenosis	Additional description: Meatal stenosis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raised protein creatinine ratio (pcr)	Additional description: Raised protein creatinine ratio (pcr)		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb cramps	Additional description: Lower limb cramps		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Right leg calf pain	Additional description: Right leg calf pain		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right hip pain	Additional description: Right hip pain		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right leg musle cramps	Additional description: Right leg musle cramps		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper back pain	Additional description: Upper back pain		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (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			
Acute bronchiolitis	Additional description: Acute bronchiolitis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus	Additional description: Adenovirus		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Broncholitis	Additional description: Broncholitis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis	Additional description: Bronchiolitis		
subjects affected / exposed	4 / 262 (1.53%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abcess	Additional description: Breast abcess		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis	Additional description: Chronic sinusitis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
E coli urinary tract infection	Additional description: E coli urinary tract infection		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19	Additional description: Covid-19		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid 19	Additional description: Covid 19		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis	Additional description: Endometritis		
subjects affected / exposed	1 / 262 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteroviral meningitis	Additional description: Enteroviral meningitis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genito -urinary tract infection	Additional description: Genito -urinary tract infection		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Group b streptococcus urinary tract infection	Additional description: Group b streptococcus urinary tract infection		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	2 / 262 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected axillary abscess	Additional description: Infected axillary abscess		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral thrush	Additional description: Oral thrush		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible urinary tract infection	Additional description: Possible urinary tract infection		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible pyelonephritis	Additional description: Possible pyelonephritis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory synctial virus (rsv)	Additional description: Respiratory synctial virus (rsv)		
subjects affected / exposed	1 / 262 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus	Additional description: Respiratory syncytial virus		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection	Additional description: Respiratory tract infection		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right frontal sinusitis	Additional description: Right frontal sinusitis		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Sepsis		
subjects affected / exposed	1 / 262 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis secondary to endometritis group a streptoco	Additional description: Sepsis secondary to endometritis group a streptoco		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected sepsis	Additional description: Suspected sepsis		
subjects affected / exposed	0 / 262 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical flare	Additional description: Umbilical flare		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral meningitis	Additional description: Viral meningitis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		

subjects affected / exposed	6 / 262 (2.29%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis	Additional description: Urosepsis		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal infection	Additional description: Vaginal infection		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral illness	Additional description: Viral illness		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection	Additional description: Viral infection		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral respiratory tract infection	Additional description: Viral respiratory tract infection		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection	Additional description: Wound infection		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 262 (0.38%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive	Additional description: Failure to thrive		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia	Additional description: Hypoglycaemia		
subjects affected / exposed	3 / 262 (1.15%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal hypoglycaemia	Additional description: Neonatal hypoglycaemia		
subjects affected / exposed	2 / 262 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal hypoglycemia	Additional description: Neonatal hypoglycemia		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor feeding	Additional description: Poor feeding		
subjects affected / exposed	1 / 262 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor feeding and lethargy	Additional description: Poor feeding and lethargy		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presumed early onset sepsis	Additional description: Presumed early onset sepsis		
subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced feeding	Additional description: Reduced feeding		
subjects affected / exposed	1 / 262 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Symptomatic hypoglycaemia	Additional description: Symptomatic hypoglycaemia		

subjects affected / exposed	0 / 262 (0.00%)	1 / 263 (0.38%)	
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	Metformin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	247 / 262 (94.27%)	258 / 263 (98.10%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroids	Additional description: Fibroids		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Vascular disorders			
Facial suffusion	Additional description: Facial suffusion		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	13 / 262 (4.96%)	4 / 263 (1.52%)	
occurrences (all)	13	4	
Maternal hypotension	Additional description: Maternal hypotension		
subjects affected / exposed	2 / 262 (0.76%)	4 / 263 (1.52%)	
occurrences (all)	2	4	
Pregnancy, puerperium and perinatal conditions			
Cephalohaematoma	Additional description: Cephalohaematoma		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Decreased foetal movement	Additional description: Decreased foetal movement		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Jaundice	Additional description: Jaundice		
subjects affected / exposed	17 / 262 (6.49%)	14 / 263 (5.32%)	
occurrences (all)	17	14	
Neonatal jaundice	Additional description: Neonatal jaundice		

subjects affected / exposed	19 / 262 (7.25%)	21 / 263 (7.98%)	
occurrences (all)	21	22	
Oligohydramnios	Additional description: Oligohydramnios		
subjects affected / exposed	3 / 262 (1.15%)	4 / 263 (1.52%)	
occurrences (all)	3	4	
Post-partum haemorrhage	Additional description: Post-partum haemorrhage		
subjects affected / exposed	4 / 262 (1.53%)	0 / 263 (0.00%)	
occurrences (all)	4	0	
Reduced fetal movements	Additional description: Reduced fetal movements		
subjects affected / exposed	3 / 262 (1.15%)	1 / 263 (0.38%)	
occurrences (all)	3	1	
Reduced fetal movement	Additional description: Reduced fetal movement		
subjects affected / exposed	34 / 262 (12.98%)	38 / 263 (14.45%)	
occurrences (all)	38	41	
Reduced foetal movement	Additional description: Reduced foetal movement		
subjects affected / exposed	22 / 262 (8.40%)	26 / 263 (9.89%)	
occurrences (all)	25	29	
General disorders and administration site conditions			
Oedema	Additional description: Oedema		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences (all)	1	3	
Pedal oedema	Additional description: Pedal oedema		
subjects affected / exposed	2 / 262 (0.76%)	5 / 263 (1.90%)	
occurrences (all)	2	5	
Peripheral oedema	Additional description: Peripheral oedema		
subjects affected / exposed	17 / 262 (6.49%)	26 / 263 (9.89%)	
occurrences (all)	18	26	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	2 / 262 (0.76%)	4 / 263 (1.52%)	
occurrences (all)	2	4	
Reproductive system and breast disorders			
Breast lump	Additional description: Breast lump		
subjects affected / exposed	3 / 262 (1.15%)	1 / 263 (0.38%)	
occurrences (all)	3	1	
Cervical ectropion	Additional description: Cervical ectropion		

subjects affected / exposed	7 / 262 (2.67%)	3 / 263 (1.14%)	
occurrences (all)	7	3	
Vaginal discharge	Additional description: Vaginal discharge		
subjects affected / exposed	10 / 262 (3.82%)	8 / 263 (3.04%)	
occurrences (all)	10	8	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	9 / 262 (3.44%)	10 / 263 (3.80%)	
occurrences (all)	10	10	
Low oxygen saturation level	Additional description: Low oxygen saturation level		
subjects affected / exposed	3 / 262 (1.15%)	2 / 263 (0.76%)	
occurrences (all)	3	2	
Nasal congestion	Additional description: Nasal congestion		
subjects affected / exposed	1 / 262 (0.38%)	7 / 263 (2.66%)	
occurrences (all)	1	7	
Respiratory distress	Additional description: Respiratory distress		
subjects affected / exposed	18 / 262 (6.87%)	18 / 263 (6.84%)	
occurrences (all)	18	18	
Sore throat	Additional description: Sore throat		
subjects affected / exposed	3 / 262 (1.15%)	6 / 263 (2.28%)	
occurrences (all)	3	7	
Psychiatric disorders			
Low mood	Additional description: Low mood		
subjects affected / exposed	3 / 262 (1.15%)	1 / 263 (0.38%)	
occurrences (all)	3	1	
Postnatal depression	Additional description: Postnatal depression		
subjects affected / exposed	7 / 262 (2.67%)	3 / 263 (1.14%)	
occurrences (all)	7	3	
Investigations			
Elevated blood pressure	Additional description: Elevated blood pressure		
subjects affected / exposed	4 / 262 (1.53%)	3 / 263 (1.14%)	
occurrences (all)	4	3	
Leucocytes in urine	Additional description: Leucocytes in urine		
subjects affected / exposed	13 / 262 (4.96%)	10 / 263 (3.80%)	
occurrences (all)	14	11	
Systolic murmur	Additional description: Systolic murmur		

subjects affected / exposed	4 / 262 (1.53%)	3 / 263 (1.14%)	
occurrences (all)	4	3	
Urinary leucocytes	Additional description: Urinary leucocytes		
subjects affected / exposed	7 / 262 (2.67%)	10 / 263 (3.80%)	
occurrences (all)	7	10	
Injury, poisoning and procedural complications			
Mechanical fall	Additional description: Mechanical fall		
subjects affected / exposed	2 / 262 (0.76%)	3 / 263 (1.14%)	
occurrences (all)	2	3	
Congenital, familial and genetic disorders			
Closed sacral dimple	Additional description: Closed sacral dimple		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Click hip	Additional description: Click hip		
subjects affected / exposed	5 / 262 (1.91%)	3 / 263 (1.14%)	
occurrences (all)	5	3	
Positional talipes	Additional description: Positional talipes		
subjects affected / exposed	5 / 262 (1.91%)	7 / 263 (2.66%)	
occurrences (all)	5	7	
Sacral dimple	Additional description: Sacral dimple		
subjects affected / exposed	6 / 262 (2.29%)	7 / 263 (2.66%)	
occurrences (all)	6	7	
Cardiac disorders			
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	2 / 262 (0.76%)	4 / 263 (1.52%)	
occurrences (all)	2	4	
Fetal tachycardia	Additional description: Fetal tachycardia		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences (all)	1	4	
Foetal tachycardia	Additional description: Foetal tachycardia		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences (all)	1	3	
Maternal tachycardia	Additional description: Maternal tachycardia		
subjects affected / exposed	6 / 262 (2.29%)	10 / 263 (3.80%)	
occurrences (all)	6	11	
Neonatal tachycardia	Additional description: Neonatal tachycardia		

subjects affected / exposed	2 / 262 (0.76%)	3 / 263 (1.14%)	
occurrences (all)	2	3	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	4 / 262 (1.53%)	3 / 263 (1.14%)	
occurrences (all)	4	3	
Nervous system disorders			
Dizzy spells	Additional description: Dizzy spells		
subjects affected / exposed	0 / 262 (0.00%)	5 / 263 (1.90%)	
occurrences (all)	0	6	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	5 / 262 (1.91%)	3 / 263 (1.14%)	
occurrences (all)	5	3	
Headache	Additional description: Headache		
subjects affected / exposed	26 / 262 (9.92%)	32 / 263 (12.17%)	
occurrences (all)	30	38	
Headaches	Additional description: Headaches		
subjects affected / exposed	5 / 262 (1.91%)	5 / 263 (1.90%)	
occurrences (all)	5	5	
Migraine	Additional description: Migraine		
subjects affected / exposed	5 / 262 (1.91%)	1 / 263 (0.38%)	
occurrences (all)	6	2	
Pre-syncope	Additional description: Pre-syncope		
subjects affected / exposed	2 / 262 (0.76%)	4 / 263 (1.52%)	
occurrences (all)	2	5	
Presyncope	Additional description: Presyncope		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Sciatica	Additional description: Sciatica		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences (all)	1	3	
Syncope	Additional description: Syncope		
subjects affected / exposed	2 / 262 (0.76%)	4 / 263 (1.52%)	
occurrences (all)	2	4	

Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	42 / 262 (16.03%)	55 / 263 (20.91%)	
occurrences (all)	43	55	
Postnatal anaemia	Additional description: Postnatal anaemia		
subjects affected / exposed	10 / 262 (3.82%)	18 / 263 (6.84%)	
occurrences (all)	10	18	
Pregnancy anaemia	Additional description: Pregnancy anaemia		
subjects affected / exposed	6 / 262 (2.29%)	4 / 263 (1.52%)	
occurrences (all)	6	4	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 262 (0.38%)	4 / 263 (1.52%)	
occurrences (all)	1	4	
Worsening of pregnancy anaemia	Additional description: Worsening of pregnancy anaemia		
subjects affected / exposed	3 / 262 (1.15%)	1 / 263 (0.38%)	
occurrences (all)	3	1	
Eye disorders			
Left sticky eye	Additional description: Left sticky eye		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences (all)	1	3	
Sticky eye	Additional description: Sticky eye		
subjects affected / exposed	6 / 262 (2.29%)	6 / 263 (2.28%)	
occurrences (all)	6	6	
Visual disturbance	Additional description: Visual disturbance		
subjects affected / exposed	5 / 262 (1.91%)	0 / 263 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Abdominal cramps	Additional description: Abdominal cramps		
subjects affected / exposed	8 / 262 (3.05%)	3 / 263 (1.14%)	
occurrences (all)	8	3	
Adhesions	Additional description: Adhesions		
subjects affected / exposed	8 / 262 (3.05%)	7 / 263 (2.66%)	
occurrences (all)	8	7	
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	12 / 262 (4.58%)	17 / 263 (6.46%)	
occurrences (all)	12	17	
Gastric reflux	Additional description: Gastric reflux		

subjects affected / exposed	16 / 262 (6.11%)	16 / 263 (6.08%)	
occurrences (all)	16	16	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	12 / 262 (4.58%)	11 / 263 (4.18%)	
occurrences (all)	13	14	
Gastric upset	Additional description: Gastric upset		
subjects affected / exposed	5 / 262 (1.91%)	6 / 263 (2.28%)	
occurrences (all)	5	6	
Colic	Additional description: Colic		
subjects affected / exposed	12 / 262 (4.58%)	9 / 263 (3.42%)	
occurrences (all)	13	9	
Constipation	Additional description: Constipation		
subjects affected / exposed	12 / 262 (4.58%)	12 / 263 (4.56%)	
occurrences (all)	12	13	
Gastrointestinal upset	Additional description: Gastrointestinal upset		
subjects affected / exposed	63 / 262 (24.05%)	14 / 263 (5.32%)	
occurrences (all)	66	14	
Gi upset	Additional description: Gi upset		
subjects affected / exposed	4 / 262 (1.53%)	1 / 263 (0.38%)	
occurrences (all)	4	1	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	4 / 262 (1.53%)	3 / 263 (1.14%)	
occurrences (all)	4	3	
Lower abdominal pain	Additional description: Lower abdominal pain		
subjects affected / exposed	4 / 262 (1.53%)	3 / 263 (1.14%)	
occurrences (all)	4	3	
Nausea	Additional description: Nausea		
subjects affected / exposed	6 / 262 (2.29%)	6 / 263 (2.28%)	
occurrences (all)	6	7	
Umbilical hernia	Additional description: Umbilical hernia		
subjects affected / exposed	4 / 262 (1.53%)	1 / 263 (0.38%)	
occurrences (all)	4	1	
Toothache	Additional description: Toothache		
subjects affected / exposed	2 / 262 (0.76%)	6 / 263 (2.28%)	
occurrences (all)	2	6	
Reflux	Additional description: Reflux		

subjects affected / exposed	5 / 262 (1.91%)	3 / 263 (1.14%)	
occurrences (all)	5	3	
Silent reflux	Additional description: Silent reflux		
subjects affected / exposed	3 / 262 (1.15%)	1 / 263 (0.38%)	
occurrences (all)	3	1	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	7 / 262 (2.67%)	6 / 263 (2.28%)	
occurrences (all)	7	6	
Skin and subcutaneous tissue disorders			
Abdominal rash	Additional description: Abdominal rash		
subjects affected / exposed	2 / 262 (0.76%)	3 / 263 (1.14%)	
occurrences (all)	2	3	
Eczema	Additional description: Eczema		
subjects affected / exposed	2 / 262 (0.76%)	3 / 263 (1.14%)	
occurrences (all)	2	3	
Erythema	Additional description: Erythema		
subjects affected / exposed	3 / 262 (1.15%)	0 / 263 (0.00%)	
occurrences (all)	3	0	
Erythema toxicum	Additional description: Erythema toxicum		
subjects affected / exposed	8 / 262 (3.05%)	8 / 263 (3.04%)	
occurrences (all)	8	8	
Itch	Additional description: Itch		
subjects affected / exposed	6 / 262 (2.29%)	8 / 263 (3.04%)	
occurrences (all)	6	8	
Rash	Additional description: Rash		
subjects affected / exposed	3 / 262 (1.15%)	5 / 263 (1.90%)	
occurrences (all)	3	5	
Scar tenderness	Additional description: Scar tenderness		
subjects affected / exposed	3 / 262 (1.15%)	3 / 263 (1.14%)	
occurrences (all)	3	3	
Renal and urinary disorders			
Dysuria	Additional description: Dysuria		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences (all)	1	3	
Haematuria	Additional description: Haematuria		

subjects affected / exposed	12 / 262 (4.58%)	8 / 263 (3.04%)	
occurrences (all)	12	9	
Ketonuria	Additional description: Ketonuria		
subjects affected / exposed	28 / 262 (10.69%)	29 / 263 (11.03%)	
occurrences (all)	33	36	
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed	46 / 262 (17.56%)	40 / 263 (15.21%)	
occurrences (all)	56	54	
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	2 / 262 (0.76%)	3 / 263 (1.14%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	6 / 262 (2.29%)	5 / 263 (1.90%)	
occurrences (all)	6	5	
Lower back pain	Additional description: Lower back pain		
subjects affected / exposed	4 / 262 (1.53%)	3 / 263 (1.14%)	
occurrences (all)	4	3	
Symphysis pubis dysfunction	Additional description: Symphysis pubis dysfunction		
subjects affected / exposed	3 / 262 (1.15%)	0 / 263 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Candidiasis	Additional description: Candidiasis		
subjects affected / exposed	5 / 262 (1.91%)	3 / 263 (1.14%)	
occurrences (all)	5	3	
Bronchiolitis	Additional description: Bronchiolitis		
subjects affected / exposed	1 / 262 (0.38%)	7 / 263 (2.66%)	
occurrences (all)	1	8	
Ear infection	Additional description: Ear infection		
subjects affected / exposed	3 / 262 (1.15%)	1 / 263 (0.38%)	
occurrences (all)	3	1	
Covid-19	Additional description: Covid-19		

subjects affected / exposed	17 / 262 (6.49%)	15 / 263 (5.70%)	
occurrences (all)	23	19	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	2 / 262 (0.76%)	6 / 263 (2.28%)	
occurrences (all)	2	6	
Chest infection	Additional description: Chest infection		
subjects affected / exposed	3 / 262 (1.15%)	3 / 263 (1.14%)	
occurrences (all)	3	3	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	3 / 262 (1.15%)	4 / 263 (1.52%)	
occurrences (all)	3	4	
Head cold	Additional description: Head cold		
subjects affected / exposed	10 / 262 (3.82%)	8 / 263 (3.04%)	
occurrences (all)	10	9	
Headcold	Additional description: Headcold		
subjects affected / exposed	3 / 262 (1.15%)	4 / 263 (1.52%)	
occurrences (all)	3	4	
Maternal pyrexia	Additional description: Maternal pyrexia		
subjects affected / exposed	0 / 262 (0.00%)	10 / 263 (3.80%)	
occurrences (all)	0	10	
Oral candida	Additional description: Oral candida		
subjects affected / exposed	5 / 262 (1.91%)	1 / 263 (0.38%)	
occurrences (all)	6	1	
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	2 / 262 (0.76%)	7 / 263 (2.66%)	
occurrences (all)	2	8	
Oral thrush	Additional description: Oral thrush		
subjects affected / exposed	3 / 262 (1.15%)	1 / 263 (0.38%)	
occurrences (all)	3	1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	3 / 262 (1.15%)	3 / 263 (1.14%)	
occurrences (all)	3	3	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	1 / 262 (0.38%)	3 / 263 (1.14%)	
occurrences (all)	2	3	
Throat infection	Additional description: Throat infection		

subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	4	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	14 / 262 (5.34%)	17 / 263 (6.46%)	
occurrences (all)	16	19	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	4 / 262 (1.53%)	4 / 263 (1.52%)	
occurrences (all)	4	4	
Vaginal candidiasis	Additional description: Vaginal candidiasis		
subjects affected / exposed	10 / 262 (3.82%)	10 / 263 (3.80%)	
occurrences (all)	10	10	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	32 / 262 (12.21%)	40 / 263 (15.21%)	
occurrences (all)	39	48	
Viral respiratory tract infection	Additional description: Viral respiratory tract infection		
subjects affected / exposed	0 / 262 (0.00%)	3 / 263 (1.14%)	
occurrences (all)	0	3	
Vomiting bug	Additional description: Vomiting bug		
subjects affected / exposed	2 / 262 (0.76%)	4 / 263 (1.52%)	
occurrences (all)	2	4	
Metabolism and nutrition disorders			
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	3 / 262 (1.15%)	0 / 263 (0.00%)	
occurrences (all)	3	0	
Impaired fasting glucose	Additional description: Impaired fasting glucose		
subjects affected / exposed	1 / 262 (0.38%)	5 / 263 (1.90%)	
occurrences (all)	1	5	
Neonatal hypoglycaemia	Additional description: Neonatal hypoglycaemia		
subjects affected / exposed	10 / 262 (3.82%)	4 / 263 (1.52%)	
occurrences (all)	10	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2017	Update to inclusion criteria – removal of lower limit of gestational age (24 weeks gestation) to enter the trial as the previous wording excluded women who were diagnosed with GDM prior to 24 weeks gestation; Update to exclusion criteria of women with a fasting glucose of >7 mmol/l or a 2hr value of >11.1mmol/l to a fasting glucose of ≥ 7 or a 2hr value of ≥ 11.1, as fasting glucose values of 7mmol/l and 11.1mmol/l were not represented in previous wording of inclusion/exclusion criteria; Update to exclusion criteria to correct the typographical error in the laboratory test for moderate to severe liver dysfunction from alkaline phosphatase greater than 3 times the upper limit of normal to aspartate aminotransferase (AST) greater than 3 times the upper limit of normal; Update to Exclusion criteria of known fetal anomaly and known small for gestational age as determined by the early or mid-trimester scan amended to remove 'as determined by the early of mid-trimester scan' as some patients may be diagnosed with GDM before the early or mid-trimester scan and this may impede recruitment of these patients; Clarification of 'current' gestational hypertension as an exclusion criterion; Addition of a biobanking section to clarify that maternal biobank samples would be taken at randomisation and week 12 post randomisation and a cord blood sample would be collected at delivery; Clarification on exemptions from AE reporting as the previous protocol wording was non-specific and open to interpretation in relation to maternal events.

24 May 2019	Exclusion criterion 'known fetal anomaly' was updated to 'Major congenital malformations or an abnormality deemed unsuitable for metformin by the site PI or attending consultant' as the description of "known foetal anomaly" was vague;Addition of text describing exclusion criterion 'Small for gestational age (SGA) refers to foetal growth less than the 10th percentile (RCOG, 2014)' to add 'or if foetal growth is deemed unsatisfactory by the treating obstetrician';Update to the 4-week post-partum visit window from (+/- 5 days) to (+/- 7 days) to accommodate weekend days;Reference from two to three trial sites updated;Clarification of definition for neonatal hypoglycaemia;Removal of reference to herbal and vitamin supplements as concomitant medications;Removal of bio-banking section from the main EMERGE protocol;Collection of physical measurements and vital signs aligned to the primary outcome visits at 32 and 38 weeks gestation;Option of a telephone visit for those pre-natal visits that did not require an in person physical measurement, laboratory assessment or drug dispensation;Height and weight measurements of baby removed from the 12 week post-partum visit;Medical history list for documentation of conditions was rationalised as some were already included in exclusion criteria/previously recorded outcomes;clarification on the options around withdrawal of consent and withdrawal from study treatment;Update to prior and concomitant therapy list of medications required to be recorded;Clarification and additional information added for valid SAE criteria, evaluation and reporting timelines to ensure clarity for site on responsibilities and requirements;Addition of list of exemptions to safety reporting for events considered common in pregnancy/postpartum period and those which must be captured as outcomes;Estimate of annual diagnosis figures of GDM updated to include relevant delivery figures from additional study sites referenced in this protocol update.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported