Clinical trial results:
Does metformin improve pregnancy outcomes [incidence of LGA (90% birth weight centile) babies onset of maternal Gestational Diabetes, hypertension, PET, shoulder dystocia, admission to SCBU) in obese non-diabetic women?

Summary

EudraCT number	2008-005892-83
Trial protocol	GB
Global end of trial date	21 August 2015

Results information

Result version number	v1 (current)
This version publication date	11 June 2016
First version publication date	11 June 2016

Trial information

Trial identification

Sponsor protocol code	WCH/2008/001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01273584
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Epsom and St Helier University Hospitals NHS Trust
Sponsor organisation address	St Helier Hospital, Wrythe Lane, carshalton, Surrey, Carshalton, Surrey, United Kingdom, SM5 1AA
Public contact	Jyoti Balani, Epsom and St Helier University Hospitals NHS Trust, 44 0208296 2140, jyoti.balani@esth.nhs.uk
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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	20 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

There is substantial evidence that obesity in pregnancy contributes to increased morbidity and mortality for both mother and baby. The purpose of the study is whether management of obese non-diabetic pregnant women with standarised lifestyle intervention (diet and physical activity) and metformin will lead to improve maternal and peri-natal outcomes compared to lifestyle intervention alone. We aim to compare peri-natal outcomes in women randomised to the two home glucose monitoring protocols:
Group 1 - Standardised lifestyle intervention and placebo.
Group 2 - Standardised lifestyle intervnetion and metformin.

Protection of trial subjects:

The dose of Metformin?placebo given was gradually increased by 1 tablet every week so that the gastric side effects were minimum.

Background therapy:

Low glycaemic index carbohydrate diet and regular excercise was recommended to all patients

Evidence for comparator:

It was a placebo controlled trial and placebo which matched Metformin were manufactured

Actual start date of recruitment	12 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 450
Worldwide total number of subjects	450
EEA total number of subjects	450

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)	450
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

October 2010 to June 2015 at 3 NHS Hospitals in the UK
Epsom and St Helier Hospitals
Kings College Hospital,
Medway Maritime Hospital

Pre-assignment

Screening details:

1071 pregnant women with BMI>35 were screened.
227 women were excluded - 6 were < 18 years of age, 17 had fetus with fetal defect, 66 had history of previous GDM, 18 had medical problems, 6 had gastric bypass, 68 had hyperemesis, 25 were receiving metformin, 8 could not take metformin and 13 had miscarriage

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Subject

Blinding implementation details:

Central randomisation was used and patients were given consecutive numbered boxes

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin arm

Arm description:

Metformin tablets

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

Dosage and administration details:

Metfromin 500 mg started as 1 tablet twice a day and gradually increased by 1 tablet every week to acheive a maximum dose of 2 tablets 3 times a day

Arm title	Placebo arm

Arm description:

Placebo tablets manufactured to look identical to the active comparator Metformin

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:

Same as Metformin

Number of subjects in period 1	Metformin arm	Placebo arm
Started	225	225
Completed	202	198
Not completed	23	27
Consent withdrawn by subject	23	27

Baseline characteristics

Reporting groups	
Reporting group title	Metformin arm
Reporting group description:	
Metformin tablets	
Reporting group title	Placebo arm
Reporting group description:	
Placebo tablets manufactured to look identical to the active comparator Metformin	

Reporting group values	Metformin arm	Placebo arm	Total
Number of subjects	225	225	450
Age categorical			
Pregnant woman with BMI>35 were recruited			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	32.9	30.8	
inter-quartile range (Q1-Q3)	27.3 to 36.2	26.6 to 34.4	-
Gender categorical			
All were female			
Units: Subjects			
Female	225	225	450
Male	0	0	0
Body Mass Index			
All women with BMI>35 kg/m2 were recruited			
Units: Kg/m2			
median	38.6	38.4	
inter-quartile range (Q1-Q3)	36.5 to 41.5	16.3 to 41.9	-

End points

End points reporting groups

Reporting group title	Metformin arm
Reporting group description: Metformin tablets	
Reporting group title	Placebo arm
Reporting group description: Placebo tablets manufactured to look identical to the active comparator Metformin	

Primary: Median birth weight percentile

End point title	Median birth weight percentile
End point description:	
End point type	Primary
End point timeframe: At the time of birth of the baby	

End point values	Metformin arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	198		
Units: KG				
median (inter-quartile range (Q1-Q3))				
Reduction in birth weight centile by 0.3SD	51.8 (23.9 to 82.1)	56.6 (26.8 to 81.4)		

Statistical analyses

Statistical analysis title	Intention to treat
Comparison groups	Metformin arm v Placebo arm
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Wilcoxon (Mann-Whitney)

Primary: Median birth weight percentile

End point title	Median birth weight percentile
End point description: The birthweight dentile of the baby is calculated for all babies	

End point type	Primary

End point timeframe:

End of the trial

End point values	Metformin arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	198		
Units: percentage				
median (inter-quartile range (Q1-Q3))				
Reduction in the birth weight z score by 0.3 D	51.8 (23.9 to 82.1)	56.6 (26.8 to 81.4)		

Statistical analyses

Statistical analysis title	Intention to treat principle

Statistical analysis description:

Comparisons between groups were perfdormed with the use of Mann-Whitney U test

Comparison groups	Metformin arm v Placebo arm
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.66 [2]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Notes:

[1] - Intention to treat analysis

[2] - Not signifiant

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the Trial	
Adverse event reporting additional description:	
Reporting of adverse events at each visit, reporting immediately in case of hospital admission	
Assessment type	Systematic

Dictionary used	
Dictionary name	Clinical terms
Dictionary version	Nil

Reporting groups	
Reporting group title	Metformin arm
Reporting group description:	
Metformin tablets	
Reporting group title	Placebo arm
Reporting group description:	
Placebo tablets manufactured to look identical to the active comparator Metformin	

Serious adverse events	Metformin arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 202 (10.40%)	38 / 198 (19.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Fetal death			
subjects affected / exposed	1 / 202 (0.50%)	5 / 198 (2.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 5	
Fetal defect			
subjects affected / exposed	3 / 202 (1.49%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fetal disease			
subjects affected / exposed	2 / 202 (0.99%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maternal disease			

subjects affected / exposed	6 / 202 (2.97%)	6 / 198 (3.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Preeclampsia or fetal growth restriction			
subjects affected / exposed	2 / 202 (0.99%)	5 / 198 (2.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Preterm births			
subjects affected / exposed	7 / 202 (3.47%)	10 / 198 (5.05%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal bleeding			
subjects affected / exposed	0 / 202 (0.00%)	5 / 198 (2.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4.2 %

Non-serious adverse events	Metformin arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 202 (50.99%)	62 / 198 (31.31%)	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	21 / 202 (10.40%)	10 / 198 (5.05%)	
occurrences (all)	21	10	
Lethargy, Constipation, Loss of apetite			
subjects affected / exposed	15 / 202 (7.43%)	9 / 198 (4.55%)	
occurrences (all)	15	9	
Gastrointestinal disorders			
Nausea and vomiting			
subjects affected / exposed	57 / 202 (28.22%)	38 / 198 (19.19%)	
occurrences (all)	57	38	
Diarrhoea			

subjects affected / exposed	35 / 202 (17.33%)	13 / 198 (6.57%)	
occurrences (all)	35	13	
Abdominal pain or heartburn			
subjects affected / exposed	14 / 202 (6.93%)	14 / 198 (7.07%)	
occurrences (all)	14	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2009	To make the trial a multicentre one To include blood tests like Fasting Insulin
20 November 2009	Increase in Sample size
20 November 2009	Change in the composition of the placebo
15 June 2010	Addition of Clinical Trial infiormation card Addition of medicine escalation sheet
25 August 2011	Sample size revised to 400
10 May 2013	Change of Principal Investigator at 1 site
23 September 2013	Shipment of blood samples from one hospital site to another for storage
20 October 2014	Addition of 50 more patients- Total 450 Addition of Epworth sleepiness scale

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 January 2012	Time required for manufacture of new batch of placebo-delay in the manufacturing pharmacy unit	04 February 2013
24 January 2014	Interupption due to delay in the manufactureof placebo by the pharmacy	04 April 2014

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Nil

Notes: