



Clinical trial results:

Pregnancy And chronic hypertension: NifeDipine or labetalol as Antihypertensive treatment

Summary

EudraCT number	2013-003144-23
Trial protocol	GB
Global end of trial date	18 May 2016

Results information

Result version number	v1 (current)
This version publication date	03 October 2018
First version publication date	03 October 2018
Summary attachment (see zip file)	PANDA PUBLICATION (publication HYPERTENSION.pdf)

Trial information

Trial identification

Sponsor protocol code	PANDA
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Additional study identifiers

ISRCTN number	ISRCTN40973936
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Lucy Chappell, King's College London, 44 0207188 3639, lucy.chappell@kcl.ac.uk
Scientific contact	Lucy Chappell, King's College London, 44 0207188 3639, lucy.chappell@kcl.ac.uk
Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE19RT
Public contact	Lucy Chappell, Guy's and St Thomas' NHS Foundation Trust, 44 0207188 3639, lucy.chappell@kcl.ac.uk
Scientific contact	Lucy Chappell, Guy's and St Thomas' NHS Foundation Trust, 44 0207188 3639, lucy.chappell@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2016
Global end of trial reached?	Yes
Global end of trial date	18 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To undertake a feasibility study for a randomised controlled trial comparing labetalol and nifedipine in pregnant women with chronic hypertension, with planned assessment of ethnic variation in drug response

Protection of trial subjects:

Routine clinical blood tests are normally taken at 12 weeks, 20 weeks, 28 weeks, on admission/around the time of delivery and 6 weeks postnatally, with additional bloods taken at other times in this high risk population given their increased risk of pre-eclampsia.

Participants will be reviewed by an appropriate clinician within two weeks of commencing the trial treatment.

Three BP measurements will be taken at each clinical visit to ensure blood pressure is suitably controlled.

Background therapy:

N/A

Evidence for comparator:

There is currently disparity regarding antihypertensive use in chronic hypertension in pregnancy in the UK and internationally. There are sufficient data to recommend avoidance of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs), which are recommended by NICE for first line use outside pregnancy in White Europeans. Antihypertensive drugs commonly used in pregnancy include labetalol, calcium channel blockers (nifedipine or amlodipine) and methyldopa. Only labetalol holds a licence for use in pregnancy before 20 weeks gestation, but this is primarily a reflection of the difficulties surrounding licensing drugs for use in pregnancy and the manufacturers of Labetalol advise avoidance in the first trimester.

Nifedipine is a calcium channel blocker which blocks the voltage-gated calcium channels in cardiac muscle and blood vessels. A decrease in cellular calcium results in less contraction of the vascular smooth muscle and therefore vasodilation. Side-effects include headache, oedema, flushing, and fatigue. Nifedipine does not hold a licence for use before 20 weeks gestation due to animal data suggesting teratogenic risk, but this increased risk has not been observed in human pregnancy. Both labetalol and nifedipine are already widely used in obstetric practice. The 2010 NICE guidance also states that there are 'no obvious associations with congenital abnormalities' for either drug

Actual start date of recruitment	21 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 114
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Worldwide total number of subjects	114
EEA total number of subjects	114

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)	114
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between 21/08/2014 and 8/05/2016. Participants were recruited from ante natal clinics within the UK.

Pre-assignment

Screening details:

Participants were eligible to participate in the trial with singleton pregnancy, aged ≥ 18 rs and have chronic hypertension - defined as diastolic BP ≥ 90 mmHg present at booking or before 20 weeks' gestation, or requiring treatment outside pregnancy and/or at time of referral) Gestation 12-27+6 weeks' at recruitment. 285 Participants were screened.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Participants were randomised to receive oral Labetalol 100mg twice per day increasing to 100mg three times per day (TDS) then to 200mg, then 300mg, then 400mg, with a maximum of 600mg TDS (1800mg/day).

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

Dosage and administration details:

Oral Labetalol 100mg twice per day increasing to 100mg three times per day (TDS) then to 200mg, then 300mg, then 400mg, with a maximum of 600mg TDS (1800mg/day).

Arm title	Group B
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Arm description:

Participants were randomised to receive oral Nifedipine Modified Release (MR) 10mg twice per day (BD) increasing to 20mg, then 30mg, with a maximum dose of 40mg BD (80mg/day).

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

Dosage and administration details:

Oral Nifedipine Modified Release (MR) 10mg twice per day (BD) increasing to 20mg, then 30mg, with a maximum dose of 40mg BD(80mg/day)

Number of subjects in period 1	Group A	Group B
Started	56	58
Completed	55	57
Not completed	1	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Group A
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Reporting group description:

Participants were randomised to receive oral Labetalol 100mg twice per day increasing to 100mg three times per day (TDS) then to 200mg, then 300mg, then 400mg, with a maximum of 600mg TDS (1800mg/day).

Reporting group title	Group B
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Reporting group description:

Participants were randomised to receive oral Nifedipine Modified Release (MR) 10mg twice per day (BD) increasing to 20mg, then 30mg, with a maximum dose of 40mg BD (80mg/day).

Reporting group values	Group A	Group B	Total
Number of subjects	56	58	114
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	56	58	114
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Females with singleton pregnancy			
Units: years			
median	36	35	
full range (min-max)	32.0 to 39.1	33.0 to 38.5	-
Gender categorical			
Units: Subjects			
Female	56	58	114
Male	0	0	0

End points

End points reporting groups

Reporting group title	Group A
Reporting group description: Participants were randomised to receive oral Labetalol 100mg twice per day increasing to 100mg three times per day (TDS) then to 200mg, then 300mg, then 400mg, with a maximum of 600mg TDS (1800mg/day).	
Reporting group title	Group B
Reporting group description: Participants were randomised to receive oral Nifedipine Modified Release (MR) 10mg twice per day (BD) increasing to 20mg, then 30mg, with a maximum dose of 40mg BD (80mg/day).	

Primary: Primary Process Endpoint

End point title	Primary Process Endpoint ^[1]
End point description: Number of participants recruited per site per month	
End point type	Primary
End point timeframe: Recruitment phase of the trial.	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This is a feasibility trial.	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	58		
Units: whole	56	58		

Attachments (see zip file)	Primary Process Endpoint/PANDA results Summary of
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Statistical analyses

No statistical analyses for this end point

Primary: Primary Clinical Endpoint

End point title	Primary Clinical Endpoint ^[2]
End point description: Highest systolic BP post-randomisation	
End point type	Primary
End point timeframe: Entire duration of trial post dosing.	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a feasibility trial

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: mmHG				
number (not applicable)	55	57		

Attachments (see zip file)	Primary Clinical Endpoint/Effect of Treatment on Brachial Blood
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Statistical analyses

No statistical analyses for this end point

Secondary: Maternal & Perinatal Outcomes

End point title	Maternal & Perinatal Outcomes
End point description:	
Maternal and perinatal morbidity	
•Acceptability (adherence to dosing regimen,side-effects of drugs and participant satisfaction)	
•Health resource use (attendances andadmissions)	
•Explanatory biomarker and vascular function assessments	
End point type	Secondary
End point timeframe:	
Throughout duration of participation in trial	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: whole	55	57		

Attachments (see zip file)	Secondary Maternal & Perinatal Outcomes/Secondary Maternal
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From recruitment until 6 week post natal visit.

Adverse event reporting additional description:

Adverse events were analysed in all randomised patients including those lost to follow-up.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Group A
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Reporting group description:

Participants were randomised to receive oral Labetalolol 100mg twice per day increasing to 100mg three times per day (TDS) then to 200mg, then 300mg, then 400mg, with a maximum of 600mg TDS (1800mg/day).

Reporting group title	Group B
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Reporting group description:

Participants were randomised to receive oral Nifedipine Modified Release (MR) 10mg twice per day (BD) increasing to 20mg, then 30mg, with a maximum dose of 40mg BD (80mg/day).

Serious adverse events	Group A	Group B	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 56 (1.79%)	3 / 58 (5.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Epistaxis	Additional description: Unplanned admission to hospital		
subjects affected / exposed	1 / 56 (1.79%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis	Additional description: Participant admitted to hospital with DVT		
subjects affected / exposed	0 / 56 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis enteroviral	Additional description: Participant admitted overnight to hospital.		
subjects affected / exposed	0 / 56 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Influenza like illness			
subjects affected / exposed	0 / 56 (0.00%)	1 / 58 (1.72%)	
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	Group A	Group B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 56 (37.50%)	15 / 58 (25.86%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 56 (17.86%)	11 / 58 (18.97%)	
occurrences (all)	10	11	
Dizziness			
subjects affected / exposed	5 / 56 (8.93%)	2 / 58 (3.45%)	
occurrences (all)	5	2	
Pregnancy, puerperium and perinatal conditions			
Lethargy			
subjects affected / exposed	2 / 56 (3.57%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Hot flushes			
subjects affected / exposed	1 / 56 (1.79%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
Nipple pain			
subjects affected / exposed	1 / 56 (1.79%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Epistaxis			
subjects affected / exposed	1 / 56 (1.79%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
Peripheral oedema neonatal			
subjects affected / exposed	2 / 56 (3.57%)	1 / 58 (1.72%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			

Nasal congestion subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 58 (0.00%) 0	
Eye disorders Eye spasm subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 58 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2 2 / 56 (3.57%) 2	2 / 58 (3.45%) 2 2 / 58 (3.45%) 2	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 5 1 / 56 (1.79%) 1	1 / 58 (1.72%) 1 0 / 58 (0.00%) 0	
Skin and subcutaneous tissue disorders Scalp tingling subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	0 / 58 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2014	Changes to eligibility criteria, schedule flow chart and additionally biomarker blood sampling.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Labetalol and nifedipine control mean systolic and diastolic BP to target in pregnant women with chronic hypertension. Good recruitment was demonstrated and mechanistic treatment effects observed. This study provides support for a larger definitive t

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28893900>