



Clinical trial results:

Feasibility study on the effects of postnatal enalapril on maternal cardiovascular function following preterm pre-eclampsia

Summary

EudraCT number	2017-003180-35
Trial protocol	GB
Global end of trial date	15 February 2021

Results information

Result version number	v1 (current)
This version publication date	08 April 2023
First version publication date	08 April 2023
Summary attachment (see zip file)	PICK-UP RCT manuscript (PICK-UP RCT.pdf) Observational PICK-UP manuscript (Observational PICK-UP.pdf)

Trial information

Trial identification

Sponsor protocol code	R04725
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03466333
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference:: 18/NW/0253

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Research Office, 1st Floor, Nowgen Centre, 29 Grafton Street, Manchester, United Kingdom, M13 9WU
Public contact	Sponsor's representative, Lynne Webster, +44 01612764125, research.sponsor@mft.nhs.uk
Scientific contact	Sponsor's representative, Lynne Webster, +44 01612764125, research.sponsor@mft.nhs.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	15 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2021
Global end of trial reached?	Yes
Global end of trial date	15 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Process outcome:

- Recruitment rate (number of women eligible, recruited and completing the study per month).

Primary Clinical outcome:

- Reduction in total vascular resistance (TVR) (from baseline to 6 months post-randomisation following treatment with enalapril, compared with placebo). Whilst TVR is the nominated primary endpoint for this feasibility study, the choice of primary outcome for the definitive trial remains uncertain.

Protection of trial subjects:

Women identified as being eligible for the study will be approached by a GCP-trained member of the clinical care team during a routine clinical appointment / inpatient admission and asked whether they would be willing to consider taking part in the study. Interested women will then have the opportunity to read through this information and further discuss the study with trial personnel. Women will then be screened against the inclusion criteria and if appropriate for inclusion and agreed to, written informed consent will be obtained.

ACE inhibitors are renally excreted and therefore must be titrated to renal function. For this reason, women will have their renal function checked prior to commencing treatment and dose increments. ACE inhibitors are contraindicated in pregnancy but are safe with breastfeeding. Most of the safety data relating to the use of ACE inhibitors when breastfeeding relate to enalapril and captopril. Because enalapril is an antihypertensive that is excreted in breastmilk, there is a theoretical concern about associated neonatal hypotension in small premature babies. Premature small babies will be routinely monitored on the neonatal unit and therefore their vital signs, including BP, will be measured during their admission. NICE guidelines support the use of enalapril for breastfeeding mothers.

Data will be collected in accordance with the "Caldicott Principles" and Data Protection Act. All women recruited will be allocated a study number which will be linked to their identifiable information held in a separate file stored within the research unit. Outcome data will be collected using case record forms which will be within stored within the Maternal & Fetal Health Research Centre (MFHRC), Manchester. All outcome data will be entered onto a password protected database within the MFHRC, accessible only to members of the research team. All electronic data will be anonymised and no identifiable data will be stored on this database.

Background therapy: -

Evidence for comparator:

This study builds on recent data, which have highlighted the relationship between pre-eclampsia (PE) and postnatal (PN) heart and vessel dysfunction and long-term heart disease risk. Enalapril is an ACE inhibitor whose use is well-established in protecting the heart outside of the setting of pregnancy / PE. In previous studies, enalapril at similar doses has been well tolerated and effective at improving long-term health in people with and at-risk of heart and vessel disease. However it has never been tested in the context of PE.

This study aims to deliver an intervention to women who have had preterm PE (pPE) during the early PN period when heart protection is likely to be most effective. Women who have persistent PN heart and vessel dysfunction are at highest risk of developing PE in their subsequent pregnancy. It is possible that continued treatment with enalapril beyond the first 6 months would be beneficial but this is beyond the scope of the current study.

The study design will be the first of its kind to address whether PN treatment with enalapril will improve heart and vessel structure and function in women who have had pPE. Its design is informed by information from observational PN studies and clinical trials in non-pregnant individuals. The present study will provide essential clinical and biochemical data necessary to determine whether future longer-term PN treatment with enalapril might be warranted. It will also determine whether there are any adverse outcomes (e.g. excessive reduction in the mother's/ baby's blood pressure) that might preclude its usefulness as a therapeutic approach in the PN period, as well as identifying any recruitment, effectiveness and acceptability issues.

Actual start date of recruitment	05 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 100
Worldwide total number of subjects	100
EEA total number of subjects	0

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)	100
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Women identified as being eligible for the study will be approached by a GCP-trained member of the clinical care team during a routine clinical appointment. Interested women will then have the opportunity to read through this information and further discuss the study with trial personnel.

Pre-assignment

Screening details:

Potential participants may be identified through screening of relevant patient information against eligibility criteria by members of the primary care team.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This is a double-blinded, randomised controlled feasibility study. Block randomisation will be done in advance by the Clinical Trials Pharmacy. The Trials pharmacy will hold a copy of the randomisation list. Both the participant and the members of the research team assessing the clinical outcomes will be blinded to the treatment arm. There will be equal allocation between treatment arms.

Arms

Are arms mutually exclusive?	Yes
Arm title	Enalapril

Arm description: -

Arm type	Experimental
Investigational medicinal product name	UKPAR enalapril maleate
Investigational medicinal product code	PL:21880/0003-5
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In this study a maximum of 20mg once daily (OD) will be given. Initially participants will take 5mg OD for 1 week then 10mg OD for 2 weeks then 20mg OD for 23 weeks (Total 6 month treatment).

Arm title	Placebo
------------------	---------

Arm description: -

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

Dosage and administration details:

N/A

Arm title	Observational
------------------	---------------

Arm description: -

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Enalapril	Placebo	Observational
Started	30	30	40
Completed	29	30	39
Not completed	1	0	1
Consent withdrawn by subject	1	-	-
Physician decision	-	-	1

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Block randomisation will be done in advance by the Clinical Trials Pharmacy. The Trials pharmacy will hold a copy of the randomisation list. Both the participant and the members of the research team assessing the clinical outcomes will be blinded to the treatment arm. There will be equal allocation between treatment arms.

Arms

Are arms mutually exclusive?	Yes
Arm title	Enalapril

Arm description: -

Arm type	Experimental
Investigational medicinal product name	UKPAR enalapril maleate
Investigational medicinal product code	PL:21880/0003-5
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In this study a maximum of 20mg once daily (OD) will be given. Initially participants will take 5mg OD for 1 week then 10mg OD for 2 weeks then 20mg OD for 23 weeks (Total 6 month treatment).

Arm title	Placebo
------------------	---------

Arm description: -

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

Dosage and administration details:

N/A

Arm title	Observational
------------------	---------------

Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Enalapril	Placebo	Observational
Started	29	30	39
Completed	19	21	23
Not completed	10	9	16
Adverse event, serious fatal	1	-	-
Physician decision	1	-	-
Consent withdrawn by subject	5	4	-
Adverse event, non-fatal	1	-	-
Pregnancy	1	-	3
Pandemic	-	-	8
Lost to follow-up	1	5	5

Baseline characteristics

Reporting groups

Reporting group title	Enalapril
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Observational
Reporting group description: -	

Reporting group values	Enalapril	Placebo	Observational
Number of subjects	30	30	40
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)	30	30	40
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
geometric mean	34.5	30.9	31.7
standard deviation	± 6.0	± 6.6	± 6.5
Gender categorical			
All participants were female			
Units: Subjects			
Female	30	30	40
Male	0	0	0

Reporting group values	Total		
Number of subjects	100		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	100		
From 65-84 years	0		
85 years and over	0		

Age continuous			
Units: years			
geometric mean			
standard deviation	-		
Gender categorical			
All participants were female			
Units: Subjects			
Female	100		
Male	0		

End points

End points reporting groups

Reporting group title	Enalapril
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Observational
Reporting group description: -	
Reporting group title	Enalapril
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Observational
Reporting group description: -	

Primary: Recruitment rate (number of women eligible, recruited and completing the study per month)

End point title	Recruitment rate (number of women eligible, recruited and completing the study per month) ^[1]
End point description: Recruitment rate (number of women eligible, recruited and completing the study per month)	
End point type	Primary
End point timeframe: Month	

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 process outcome and therefore only descriptive stats were required as no comparator.

End point values	Enalapril	Placebo	Observational	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	30	39	
Units: women				
number (not applicable)	1.1	1.2	1.0	

Statistical analyses

No statistical analyses for this end point

Primary: Change in TVR from baseline to six months post randomisation following treatment with enalapril, compared with placebo

End point title	Change in TVR from baseline to six months post randomisation following treatment with enalapril, compared with placebo
End point description: Change in TVR from baseline to six months post randomisation following treatment with enalapril, compared with placebo	

End point type	Primary
End point timeframe:	
6 months	

End point values	Enalapril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: dyne.s-1cm-5				
arithmetic mean (standard deviation)	1516 (± 278)	1579 (± 438)		

Statistical analyses

Statistical analysis title	Change in TVR from baseline to six months post ran
Comparison groups	Enalapril v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence ^[2]
P-value	= 0.59
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Notes:

[2] - Standard ANCOVA with baseline measurements as a covariate

Secondary: Change in remodelling from baseline to six months post randomisation following treatment with enalapril, compared with placebo

End point title	Change in remodelling from baseline to six months post randomisation following treatment with enalapril, compared with placebo
-----------------	--

End point description:

Change in remodelling from baseline to six months post randomisation following treatment with enalapril, compared with placebo

End point type	Secondary
----------------	-----------

End point timeframe:

6 months

End point values	Enalapril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: g/m2				
arithmetic mean (standard deviation)	64.90 (± 14.93)	71.91 (± 17.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in diastolic dysfunction from baseline to six months post randomisation following treatment with enalapril, compared with placebo

End point title	Change in diastolic dysfunction from baseline to six months post randomisation following treatment with enalapril, compared with placebo
End point description: Change in diastolic dysfunction from baseline to six months post randomisation following treatment with enalapril, compared with placebo	
End point type	Secondary
End point timeframe: 6 months	

End point values	Enalapril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: ratio				
arithmetic mean (standard deviation)	6.41 (\pm 2.03)	7.48 (\pm 1.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in diastolic blood pressure (dBp) from baseline to six months post randomisation following treatment with enalapril, compared with placebo

End point title	Change in diastolic blood pressure (dBp) from baseline to six months post randomisation following treatment with enalapril, compared with placebo
End point description: Change in diastolic blood pressure (dBp) from baseline to six months post randomisation following treatment with enalapril, compared with placebo	
End point type	Secondary
End point timeframe: 6 months	

End point values	Enalapril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: mmHg				
arithmetic mean (standard deviation)	79.6 (± 10.9)	86.9 (± 10.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the duration of the trial

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	1
--------------------	---

Reporting groups

Reporting group title	Enalapril
-----------------------	-----------

Reporting group description: -

Reporting group title	Placebo
-----------------------	---------

Reporting group description: -

Reporting group title	Observational
-----------------------	---------------

Reporting group description: -

Serious adverse events	Enalapril	Placebo	Observational
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	0 / 40 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Left ventricular failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

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

Non-serious adverse events	Enalapril	Placebo	Observational
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	0 / 30 (0.00%)	0 / 40 (0.00%)
Nervous system disorders			

Seizure subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 30 (0.00%) 0	0 / 40 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	0 / 30 (0.00%) 0	0 / 40 (0.00%) 0
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 30 (0.00%) 0	0 / 40 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2018	<ol style="list-style-type: none">1. Inclusion of angio-oedema as a potential side-effect in the Participant Information Sheet (PIS)2. Extension of the 6 month visit window to 6 months+/-2 weeks3. Collection of urine at 6 weeks and 6 months to measure Enalapril compliance4. Correction of typographical errors in the protocol5. Addition of urinary measures of Enalapril compliance & attendance at each research visit to the statistical analysis plan.6. Removal of the breast milk analysis from the consent form, PIS and protocol
07 January 2019	<ol style="list-style-type: none">1. An additional IMP re-supply visit (if required) between visits 4 and 5. This is due to the length (23 weeks) of the final 20mg prescription and the expiry date of the study drug/placebo (June 2019). We have added this additional visit to re-supply participants with new IMP stock and avoid the risk of patients having expired IMP at home.2. An increase in the number of participants in the interventional arm from 36 evaluable to 40.3. An additional investigation added at visit 5: breastfeeding status and duration of breastfeeding.4. A typographical correction to section 18 of the protocol.
05 November 2019	<ol style="list-style-type: none">1. "A change in Nitric Oxide end products (NOx)" has been removed from the secondary outcome measures as the study team considered the results unlikely to be useful in the content of this feasibility study.2. The definition of the end of study has changed to "the date of complete database lock following the final research visit"3. The name of the sponsor representative has been changed to Dr Lynne Webster following the departure of Dr Griffin from the trust in October 2019.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33012200>

<http://www.ncbi.nlm.nih.gov/pubmed/36029727>