



## Clinical trial results: Paracetamol Treatment in Hypertension: effect on Blood Pressure Study.

### Summary

EudraCT number	2013-003204-40
Trial protocol	GB
Global end of trial date	01 February 2022

### Results information

Result version number	v1 (current)
This version publication date	05 October 2023
First version publication date	05 October 2023

### Trial information

#### Trial identification

Sponsor protocol code	PATHBP_2013
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01997112
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	ACCORD (University of Edinburgh and NHS Lothian)
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Prof David Webb, University of Edinburgh, +44 01312429216, D.J.Webb@ed.ac.uk
Scientific contact	Prof David Webb, University of Edinburgh, +44 01312429216, D.J.Webb@ed.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	01 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2022
Global end of trial reached?	Yes
Global end of trial date	01 February 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine the effect of paracetamol on blood pressure in hypertensives adults taking or not taking antihypertensive medications.

Protection of trial subjects:

The trial was conducted in accordance with all relevant data protection, ethical and regulatory requirements to ensure the privacy and security of patient information and to ensure the rights, safety and well-being of the patients and the quality of the research data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2014
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: 110
Worldwide total number of subjects	110
EEA total number of subjects	110

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)	66
From 65 to 84 years	44
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Between September 2014 and June 2019 204 patients were identified through: the hypertension service in Edinburgh; NHS Lothian GP Practices; GP ABPM service; SHARE (NHS Research Scotland initiative - to search for willing participants in the SE Scotland). 110 of these were randomised into the trial.

### Pre-assignment

Screening details:

Participant's medical history & medication use will be reviewed. Complete physical examination: height, weight, vital signs. Blood taken for full blood count, paracetamol level, coagulation screen, INR, liver, renal function. Participants asked to wear a 24-hour ambulatory blood pressure monitor, if ABPM has not been performed in previous 3 months.

### Period 1

Period 1 title	Baseline (overall trial) (Studies 1 + 2)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Paracetamol

Arm description:

Paracetamol 1g (500mg x2) four times daily, given for 14 days, with a 14-day washout period. (Cross-over trial.)

Arm type	Active comparator
Investigational medicinal product name	Paracetamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1g (500mg x 2) four times daily.

<b>Arm title</b>	Placebo
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Arm description:

Placebo: hard gelatin capsules containing Maize Starch Ph. Eur.

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

Dosage and administration details:

Two capsules, four times per day. There is a washout phase of 14(+7) days between treatment phases.

<b>Number of subjects in period 1</b>	Paracetamol	Placebo
Started	55	55
Completed	53	50
Not completed	2	5
Consent withdrawn by subject	2	-
Physician decision	-	5

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## Period 2

Period 2 title	Sub-study: biomarker study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

<b>Arm title</b>	Sub-study: biomarker study
Arm description:	
All participants will be asked to participate in this sub-study. One extra blood sample will be taken at each study visit (10mls) for liver function tests and biomarker analyses. In addition, a blood sample (5mls) will be taken on day 1 for DNA analysis.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 2</b>	Sub-study: biomarker study
Started	103
Completed	103

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## Period 3

Period 3 title	Sub-study: urinary prostaglandins study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

<b>Arm title</b>	Sub-study: urinary prostaglandins study
Arm description: All females taking part in the baseline studies 1 and 2 will be asked to provide a 24-hour urine collection for PGE and 6-keto-PGF $\alpha$ estimation. A 24-hour urine collection will be performed on four occasions throughout the study, at the start and end of each study drug period.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 3<sup>[1]</sup></b>	Sub-study: urinary prostaglandins study
Started	17
Completed	17

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of the 17 subjects actually enrolled into the sub-study - 17 started this sub-study and 17 completed the sub-study

## Baseline characteristics

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### Reporting groups

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Reporting group title	Baseline (overall trial) (Studies 1 + 2)
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Reporting group description: -

<b>Reporting group values</b>	Baseline (overall trial) (Studies 1 + 2)	Total	
Number of subjects	110	110	
Age categorical Units: Subjects			
Adults (18-64 years)	66	66	
From 65-84 years	44	44	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	26	26	
Male	84	84	

## End points

### End points reporting groups

Reporting group title	Paracetamol
Reporting group description: Paracetamol 1g (500mg x2) four times daily, given for 14 days, with a 14-day washout period. (Cross-over trial.)	
Reporting group title	Placebo
Reporting group description: Placebo: hard gelatin capsules containing Maize Starch Ph. Eur.	
Reporting group title	Sub-study: biomarker study
Reporting group description: All participants will be asked to participate in this sub-study. One extra blood sample will be taken at each study visit (10mls) for liver function tests and biomarker analyses. In addition, a blood sample (5mls) will be taken on day 1 for DNA analysis.	
Reporting group title	Sub-study: urinary prostaglandins study
Reporting group description: All females taking part in the baseline studies 1 and 2 will be asked to provide a 24-hour urine collection for PGE and 6-keto-PGF $\alpha$ estimation. A 24-hour urine collection will be performed on four occasions throughout the study, at the start and end of each study drug period.	

### Primary: Difference in mean daytime systolic ambulatory BP

End point title	Difference in mean daytime systolic ambulatory BP <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe: Study: day 1 (visit -1), day 5 (visit 4), day 8 (visit 7) and day 15 (visit 14). Cross-over: day 29 (visit -1), day 33 (visit 4), day 36 (visit 7) and day 43 (visit 14).	
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: Arithmetic mean Precision/Dispersion Type: Standard deviation Difference in least square mean: 4.7 Confidence interval: 2.9-6.6	

End point values	Paracetamol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: mmHg				
arithmetic mean (standard deviation)	4.7 ( $\pm$ 2.9)	4.7 ( $\pm$ 2.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Difference in clinic systolic BP

End point title	Difference in clinic systolic BP
End point description:	
End point type	Secondary
End point timeframe:	
Study: day 1 (visit -1), day 5 (visit 4), day 8 (visit 7) and day 15 (visit 14). Cross-over: day 29 (visit -1), day 33 (visit 4), day 36 (visit 7) and day 43 (visit 14).	

End point values	Paracetamol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	55		
Units: mmHg				
arithmetic mean (standard deviation)	4.6 (± 6.7)	4.6 (± 6.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Difference in daytime diastolic ambulatory BP

End point title	Difference in daytime diastolic ambulatory BP
End point description:	
End point type	Secondary
End point timeframe:	
Study: day 1 (visit -1), day 5 (visit 4), day 8 (visit 7) and day 15 (visit 14). Cross-over: day 29 (visit -1), day 33 (visit 4), day 36 (visit 7) and day 43 (visit 14).	

End point values	Paracetamol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	55		
Units: mmHg				
arithmetic mean (standard deviation)	1.6 (± 2.7)	1.6 (± 2.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Difference in mean daytime systolic ambulatory BP in patients taking and not taking antihypertensive medications

End point title	Difference in mean daytime systolic ambulatory BP in patients taking and not taking antihypertensive medications
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End point description:

End point type	Secondary
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End point timeframe:

Study: day 1 (visit -1), day 5 (visit 4), day 8 (visit 7) and day 15 (visit 14). Cross-over: day 29 (visit -1), day 33 (visit 4), day 36 (visit 7) and day 43 (visit 14).

End point values	Paracetamol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	55		
Units: mmHg				
arithmetic mean (standard deviation)	3.6 ( $\pm$ 11.3)	3.6 ( $\pm$ 11.3)		

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Difference in urinary prostaglandins

End point title	Difference in urinary prostaglandins
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End point description:

End point type	Other pre-specified
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End point timeframe:

Study: start 24hr urine collection (UC) study day 1, finish study day 2; start 24hr UC study day 15, finish study day 16. Crossover: start 24hr UC study day 29, finish study day 2; start 24hr UC study day 43, study day 44.

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Difference in liver biomarkers

End point title	Difference in liver biomarkers
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End point description:

End point type	Other pre-specified
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End point timeframe:

Study: day 1 (visit -1), day 5 (visit 4), day 8 (visit 7) and day 15 (visit 14). Cross-over: day 29 (visit -1), day 33 (visit 4), day 36 (visit 7) and day 43 (visit 14).

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<b>End point values</b>	Sub-study: biomarker study			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[2]</sup>			
Units: U/L				
arithmetic mean (standard deviation)	( )			

Notes:

[2] - Not analysed.

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Investigators must report all SAEs to the Sponsor within 24 hours of becoming aware of event.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Baseline (overall trial) (Studies 1 + 2)
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Reporting group description: -

<b>Serious adverse events</b>	Baseline (overall trial) (Studies 1 + 2)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 110 (1.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Baseline (overall trial) (Studies 1 + 2)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 110 (60.00%)		
Injury, poisoning and procedural complications			
Accidental injury to right thumb, requiring sutures.			

subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Broken tooth. subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Bruised ribs (left sided) post accidental injury. subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Bruised ribs - sporting accident subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Left knee injury	Additional description: Left knee injury- attending Osteopath regularly		
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Minor knee injury subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Pulled muscle (strain) right side below rib subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Left leg muscle tear subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Vascular disorders Patchy facial flushing subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Cardiac disorders Atrial Fibrillation subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Atrial Flutter subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
fluttering in his upper left chest	Additional description: Patient noted both yesterday x 3 episodes and today x 4 episodes over a six hour period - fluttering in his upper left chest. No other		

symptoms to note. Arrhythmia PMH 2011. Manual pulse taken - regular, strong and around 60 BPM. ECG performed today

subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
<b>Nervous system disorders</b>			
Dizziness/lightheaded			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Headaches			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Occasional headaches			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Right sided sciatica			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Sporadic nerve pain in left forefinger (distal joint). Possible gym injury.			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
light headed			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
poor quality sleep			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
sciatic pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Left sided sciatica			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
<b>General disorders and administration site conditions</b>			

Lump at left lymph removal site.	Additional description: Lump at left lymph removal site. Assessed. NAD.		
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Tiredness			
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Immune system disorders			
Hayfever symptoms			
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Mild hayfever symptoms of sneezing			
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Seasonal hayfever.			
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Eye disorders			
Dry eyes			
subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 2		
Red and Itchy eyes			
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Gastrointestinal disorders			
Gastric upset. Diarrhoea + vomiting x single episode			
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Heartburn			
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Indigestion			
subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 4		
Mild Nausea			
subjects affected / exposed occurrences (all)	3 / 110 (2.73%) 3		

Mild stomach ache on occasions subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Mouth ulcers subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Sporadic toothache subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
tooth pain following extraction and abscess subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Gastric upset. subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Nauseous when taking IMP subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Increased bowel movement to twice daily. subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Nausea and vomiting subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Respiratory, thoracic and mediastinal disorders			
Chesty wheeze subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Nasal congestion			

subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Patient aware of clearing throat more often.			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Sore throat			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Tickly cough			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Throat pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
exacerbation of asthma			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Left forearm lesion	Additional description: Left forearm lesion under review - GP referral to dermatology 21/01/2019 Discharged from appointment with no follow-up except pre arranged 6 monthly visits for monitoring re PMH.		
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Rash over right forearm			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
dry skin on legs and armpits			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Cellulitis/Allergic reaction/Photosensitivity			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Itching round ankles			

subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Rash on right forearm subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Urticaria subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Itchy rash on forehead & neck subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Musculoskeletal and connective tissue disorders			
Backache subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Lower back ache subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Painful left ankle subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Right Achilles tendon pain subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Right sided ache under ribs subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
right knee pain subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Lower back pain subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Slight swelling both ankles			

subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Stiffness left shoulder and neck. subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
left knee pain subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Right ankle Achilles tendon tenderness subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Infections and infestations			
Cold symptoms subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 9		
Cold symptoms - upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 2		
Gum infection followed by a tooth extraction subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Mild infection of left eye.	Additional description: Mild infection of left eye. Over the counter eye drops used and symptoms improving.		
subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Right eye conjunctivitis subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Sore throat and cold symptoms subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Viral illness. subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
upper respiratory tract infection			

subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
flu like symptoms			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported