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

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 parcetamol 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
Arm title	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.

Arm title	Placebo

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.

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Consent withdrawn by subject	2	-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

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

Arms

Arm title	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

Number of subjects in period 2	Sub-study: biomarker study
Started	103
Completed	103

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

Arm title	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-PGFα 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

Number of subjects in period 3[1]	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

Reporting groups

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

Reporting group description: -

Reporting group values	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-PGFα 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[1]
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 (± 2.9)	4.7 (± 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

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)	3.6 (± 11.3)	3.6 (± 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

End point description:

End point type	Other pre-specified

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

End point description:

End point type	Other pre-specified

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	Sub-study: biomarker study			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: U/L				
arithmetic mean (standard deviation)	()			

Notes:

[2] - Not analysed.

Statistical analyses

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

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

Reporting group description: -

Serious adverse events	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 %

Non-serious adverse events	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	1 / 110 (0.91%)		
occurrences (all)	1		
Broken tooth.			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Bruised ribs (left sided) post accidental injury.			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Bruised ribs - sporting accident			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Left knee injury	Additional description: Left knee injury- attending Osteopath regularly		
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Minor knee injury			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Pulled muscle (strain) right side below rib			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Left leg muscle tear			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Vascular disorders			
Patchy facial flushing			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Atrial Flutter			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	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		
Nervous system disorders			
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		
General disorders and administration site conditions			

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

Mild stomach ache on occasions			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Mouth ulcers			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Sporadic toothache			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
tooth pain following extraction and abscess			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Gastric upset.			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Nauseous when taking IMP			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Increased bowel movement to twice daily.			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Nausea and vomiting			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Chesty wheeze			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	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	1 / 110 (0.91%)		
occurrences (all)	1		
Rash on right forearm			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Itchy rash on forehead & neck			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Backache			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Lower back ache			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Painful left ankle			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Right Achilles tendon pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Right sided ache under ribs			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
right knee pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Lower back pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Slight swelling both ankles			

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported