Clinical trial results:
Hellenic Anglo Research into Morning Or Night antihypertensive drug deliverY trial.

Summary

EudraCT number	2011-004192-37
Trial protocol	GB
Global end of trial date	31 October 2016

Results information

Result version number	v1 (current)
This version publication date	14 May 2017
First version publication date	14 May 2017

Trial information

Trial identification

Sponsor protocol code	CRO1749

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01669928
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Joint Research Compliance Office, Imperial College London
Sponsor organisation address	Room 221, Medical school Building, St Mary's Campus, Norfolk Place, London, United Kingdom, W2 1PG
Public contact	Professor Neil Poulter, Imperial College London, +44 20 7594 3446, n.poulter@imperial.ac.uk
Scientific contact	Professor Neil Poulter, Imperial College London, +44 20 7594 3446, n.poulter@imperial.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	11 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2016
Global end of trial reached?	Yes
Global end of trial date	31 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To detect if there is a 3mm Hg difference in average 24 hour systolic blood pressure when blood pressure lowering medications are taken in the evening compared with same medications taken in the morning.

Protection of trial subjects:

No measures were required to be put into place as patients were on their usual blood pressure medications with the only change being the time of day (morning or evening) the medication should be taken.

Background therapy:

All study recruits continued on whatever drug therapy and lifestyle manoeuvres were in place before recruitment into the trial. Recruits were advised to make no changes to these interventions at any stage in the trial other than the timing of drug administration (morning or evening).

Evidence for comparator:

In order to detect a 3 mm Hg difference in mean 24 hour systolic BP (SBP) (between periods when antihypertensive medications are taken in the morning and when taken at night) with 80% power (2-sided), $p < 0.05$ and an estimated standard deviation (SD) in mean 24 hour SBP of 10 mmHg, 90 patients were needed to complete the trial. Assuming a dropout rate of approximately 10%, 100 patients in total were required to be randomized between the two centres, with 45 patients in each treatment group.

Actual start date of recruitment	23 July 2013
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: 53
Country: Number of subjects enrolled	Greece: 50
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	51
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

103 patients were recruited to the trial between July 2013 and Jan 2015, across two sites: Peart-Rose Research Unit, Imperial College London, UK and the Outpatient Clinic of 1st Medical Propedeutic Dept. of Internal Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, Greece. The the last patient last visit occurred in July 2015.

Pre-assignment

Screening details:

Suitable participants were identified at treating hospitals, research departments or the general practices by the study team. Patients were screened if they were on 2 or more stable hypertensive medications for at least 3 months prior to the study and were aged between 18-80 years.

Period 1

Period 1 title	Baseline to Crossover
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Morning/Evening

Arm description:

Patients who took their BP medication in the morning (between 06:00 and 11:00) in the first period for 12 weeks and in the evening (between 18:00 and 23:00) in the second period for another 12 weeks.

Arm type	Sequence
Investigational medicinal product name	Usual BP medication
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Usual BP medication

Arm title	Evening/Morning

Arm description:

Patients who took their BP medication in the evening (between 18:00 and 23:00) in the first period for 12 weeks and in the morning (between 06:00 and 11:00) in the second period for another 12 weeks.

Arm type	Sequence

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Morning/Evening	Evening/Morning
Started	51	52
Crossover	48	49
Completed	48	49
Not completed	3	3
Consent withdrawn by subject	2	1
Physician decision	-	1

Dropped out and rescreened	-	1
Randomised in error	1	-

Period 2	
Period 2 title	Crossover to Final Visit
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Morning/Evening

Arm description:

Patients who took their BP medication in the morning (between 06:00 and 11:00) in the first period for 12 weeks and in the evening (between 18:00 and 23:00) in the second period for another 12 weeks.

Arm type	Sequence

No investigational medicinal product assigned in this arm

Arm title	Evening/Morning

Arm description:

Patients who took their BP medication in the evening (between 18:00 and 23:00) in the first period for 12 weeks and in the morning (between 06:00 and 11:00) in the second period for another 12 weeks.

Arm type	Sequence

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Morning/Evening	Evening/Morning
Started	48	49
Completed	48	47
Not completed	0	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1

Period 3	
Period 3 title	At Final visit
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	No
Arm title	Morning
Arm description: Result for the morning admission.	
Arm type	Morning
No investigational medicinal product assigned in this arm	
Arm title	Evening
Arm description: Results for evening admission	
Arm type	Evening
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Morning	Evening
Started	103	103
Completed	98	100
Not completed	5	3
Consent withdrawn by subject	3	1
Physician decision	-	1
Adverse event, non-fatal	1	-
Dropped out and rescreened	-	1
Error randomisation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Morning/Evening
Reporting group description:	
Patients who took their BP medication in the morning (between 06:00 and 11:00) in the first period for 12 weeks and in the evening (between 18:00 and 23:00) in the second period for another 12 weeks.	
Reporting group title	Evening/Morning
Reporting group description:	
Patients who took their BP medication in the evening (between 18:00 and 23:00) in the first period for 12 weeks and in the morning (between 06:00 and 11:00) in the second period for another 12 weeks.	

Reporting group values	Morning/Evening	Evening/Morning	Total
Number of subjects	51	52	103
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	61.8	61.8	
standard deviation	± 11	± 9.7	-
Gender categorical			
Units: Subjects			
Female	24	21	45
Male	27	31	58

End points

End points reporting groups

Reporting group title	Morning/Evening
Reporting group description:	
Patients who took their BP medication in the morning (between 06:00 and 11:00) in the first period for 12 weeks and in the evening (between 18:00 and 23:00) in the second period for another 12 weeks.	
Reporting group title	Evening/Morning
Reporting group description:	
Patients who took their BP medication in the evening (between 18:00 and 23:00) in the first period for 12 weeks and in the morning (between 06:00 and 11:00) in the second period for another 12 weeks.	
Reporting group title	Morning/Evening
Reporting group description:	
Patients who took their BP medication in the morning (between 06:00 and 11:00) in the first period for 12 weeks and in the evening (between 18:00 and 23:00) in the second period for another 12 weeks.	
Reporting group title	Evening/Morning
Reporting group description:	
Patients who took their BP medication in the evening (between 18:00 and 23:00) in the first period for 12 weeks and in the morning (between 06:00 and 11:00) in the second period for another 12 weeks.	
Reporting group title	Morning
Reporting group description:	
Result for the morning admission.	
Reporting group title	Evening
Reporting group description:	
Results for evening admission	

Primary: 24 hour ABPM - mean systolic BP

End point title	24 hour ABPM - mean systolic BP
End point description:	
24 hour ABPM - mean systolic BP	
End point type	Primary
End point timeframe:	
24 hours	

End point values	Morning	Evening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: mmHg	130	130		

Statistical analyses

Statistical analysis title	Regression adjusted
Statistical analysis description:	
Includes 95 patients who had ABPMs at baseline, crossover and final visits.	

Comparison groups	Morning v Evening
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	3.42

Statistical analysis title	Observed difference[1]

Statistical analysis description:

95 patients who completed ABPMs at baseline, crossover and final visits were included in this analysis.

Comparison groups	Morning v Evening
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0

Notes:

[1] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.
Justification: The outcome is a difference and it is not specific to one group or the other but it makes sense to enter the observed values for the two groups. These are not estimates but exact numbers so there is no related confidence interval.

Primary: 24 hour ABPM - mean diastolic BP

End point title	24 hour ABPM - mean diastolic BP

End point description:

24 hour ABPM - mean diastolic BP

End point type	Primary

End point timeframe:

24 hours

End point values	Morning	Evening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	95		
Units: mmHg	77	78		

Statistical analyses

Statistical analysis title	Regression adjusted
Statistical analysis description: Includes 95 patients who had ABPMs at baseline, crossover and final visits.	
Comparison groups	Morning v Evening
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.38
upper limit	2.91

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

23rd July 2013 (date first patient enrolled) to 15th July 2015 (28 days after last patient, last visit).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Morning/Evening
Reporting group description: -	
Reporting group title	Evening/Morning
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were reported, only one three serious adverse events were reported in the trial.

Serious adverse events	Morning/Evening	Evening/Morning	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Endoscopic retrograde cholangiopancreatography	Additional description: Planned admission for ERCP with stent.		
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Syncope	Additional description: Syncope episode leading to angiogram, showing 3 vessel disease. Patient underwent cardiac bypass surgery and pacemaker insertion.		
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain	Additional description: Pain in chest radiating through back. Troponin negative, angiogram showed no aortic dissection but showed gallstone. Chest X-ray clear.		
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	
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: 0.05 %

Non-serious adverse events	Morning/Evening	Evening/Morning	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2012	Substantial amendment. Minor administrative changes to the trial protocol and patient information sheet. Submission of letter of invitation to participant and patient diary card for Ethics approval.
25 September 2012	Minor amendment. Administrative changes made to the GP letter regarding patient participation to provide information on which randomisation arm the patient has been allocated and to provide further detail of the current medication the patient is taking.
19 October 2012	Minor amendment. Administrative changes to the trial protocol, patient information sheet and consent form to clarify inconsistencies regarding ABPM measurement timings.
02 July 2013	Substantial amendment. Following sections of the protocol changed: 1) Secondary outcome Clarification that occurrence of side effects is based self reported serious adverse events to maintain consistency with the adverse events reporting section which already states this. 2) and 3) Inclusion and Exclusion Criteria Reduction of the lower accepted Diastolic Blood Pressure to 65 mmHg (instead of 75) to enhance the generalisability of the findings as our clinic database has shown this better reflects the current patient population in the clinic and therefore the population under study. 4) Treatment Schedule Further details added to the protocol and patient information sheet to clarify the questions asked and data that will be collected. 5) Sponsor Sponsor contact change from Lucy Parker to Nabila Youssouf. NB the Sponsor did not change.
23 April 2014	Minor and substantial amendments. SUBSTANTIAL AMENDMENT TO MHRA AND ETHICS Change in the inclusion criteria that previously included 'Caucasian patients [white and of European origin] aged 18-80 years' to now state 'Any patients aged 18-80 years'. This was to enhance the generalisability of the findings as the clinic database has shown this better reflects the current patient population in the clinic and therefore the population under study. MINOR AMENDMENT TO MHRA AND ETHICS In the previous amendment we informed of a change in Sponsor contact details but the details were not changed on the protocol in error, so this was been corrected in version 5 of the protocol. SUBSTANTIAL AMENDMENT TO ETHICS ONLY 1) Questionnaire designed to be given to patients at the end of the study to gain their feedback on preference for time of day for taking medication. We have attached the questionnaire for review (to ethics only) 2) Intended to contact patients who have taken part in other studies and consented to being contacted for future studies. Drafted letter and questionnaire for review (to ethics only)

19 December 2014	Minor amendments: 1) Sponsor contact details The contact person for the Sponsor changed and updated on version 6 of the protocol 2) Correction of typo On page 9, section 4.1 of the protocol which still referred to patients recruited being Caucasian. This was changed in the last substantial amendment in the inclusion/exclusion criteria on the protocol but was missed from this section in error so was now deleted 3) Change in distribution of patient recruitment. The previous version of the protocol stated that an equal number of patients will be recruited at each of the two sites for the study. As recruitment was slower at one site, recruitment would not be equal between sites and this was changed in the protocol accordingly. NB was NOT a change to the number of patients to be recruited.
11 February 2015	Minor amendment. Updated sponsor details on the protocol version 7.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported