Clinical trial results:
A randomised placebo-controlled trial of fixed-dose combination medication in those at raised risk of cardiovascular disease

Summary

EudraCT number	2007-002466-35
Trial protocol	NL GB
Global end of trial date	22 December 2009

Results information

Result version number	v1 (current)
This version publication date	16 May 2020
First version publication date	16 May 2020

Trial information

Trial identification

Sponsor protocol code	Polypill

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Australian New Zealand Clinical Trials Registry: ACTRN12607000099426

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	PROFESSOR SIMON THOM, Imperial College London, +44 (0)20 7594 1100, s.thom@imperial.ac.uk
Scientific contact	PROFESSOR SIMON THOM, Imperial College London, +44 (0)20 7594 1100, s.thom@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	22 December 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2009
Global end of trial reached?	Yes
Global end of trial date	22 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the trial is to evaluate whether a "polypill" a fixed low dose combination of blood pressure lowering drugs (an ACE inhibitor and diurectic), cholesterol lowering drugs (a statin) and asprin results in improved systolic Blood Pressue and LDL-cholesterol(bad cholesterol) levels and is tolerable compared with placebo (a tablet containing no medication) in individuals at raised risk of 7.5% or more in the next 5 years of a major cardiovascular event, such as a heart attack or stroke. (This estimate is made by considering a number of factors including your age, gender, blood pressure, cholesterol level and whether you smoke).

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2007
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	Netherlands: 102
Country: Number of subjects enrolled	United Kingdom: 113
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	India: 109
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	378
EEA total number of subjects	215

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)	261
From 65 to 84 years	117
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 17 October 2008 to 22 December 2009.

Pre-assignment

Screening details:

After screening, 481 participants were ineligible (due to too low Cv risk, did not complete the form, too high CV risk) and 378 eligible.

Period 1

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

Blinding implementation details:

Participants, research staff and and co-ordinating centre staff were all blinded to the allocation

Arms

Are arms mutually exclusive?	Yes
Arm title	Red Heart Pill

Arm description:

Participants received Red Heart Pill (RHP, a polypill comprising a bilayered tablet containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg) for 12 weeks

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

Dosage and administration details:

The polypill comprising a bilayered tablet containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg)

Arm title	Placebo

Arm description:

Participants received placebo

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

Dosage and administration details:

Tablet for 12 weeks

Number of subjects in period 1	Red Heart Pill	Placebo
Started	189	189
Completed	186	187
Not completed	3	2
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Red Heart Pill
Reporting group description:	
Participants received Red Heart Pill (RHP, a polypill comprising a bilayered tablet containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg) for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo	

Reporting group values	Red Heart Pill	Placebo	Total
Number of subjects	189	189	378
Age categorical Units: Subjects			
Adults (Age 30-80)	189	189	378
Age continuous Units: years			
arithmetic mean	61.2	61.6	
standard deviation	± 7.2	± 7.2	-
Gender categorical Units: Subjects			
Female	36	37	73
Male	153	152	305
Systolic Blood pressure Units: mm Hg			
arithmetic mean	132	136	
standard deviation	± 13	± 14	-
Diastolic blood pressure Units: mm Hg			
arithmetic mean	80	81	
standard deviation	± 9	± 9	-
LDL-cholesterol Units: mmol/L			
arithmetic mean	3.7	3.6	
standard deviation	± 0.9	± 0.9	-
Total cholesterol Units: mmol/L			
arithmetic mean	5.6	5.4	
standard deviation	± 1.1	± 1.0	-
HDL cholesterol Units: mmol/L			
arithmetic mean	1.2	1.3	
standard deviation	± 0.3	± 0.4	-

End points

End points reporting groups

Reporting group title	Red Heart Pill
Reporting group description:	
Participants received Red Heart Pill (RHP, a polypill comprising a bilayered tablet containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg) for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo	

Primary: Changes in Systolic blood pressure

End point title	Changes in Systolic blood pressure[1][2]
End point description:	
Intention-to-treat analyses.	
End point type	Primary
End point timeframe:	
12 weeks	

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: The primary analysis was by intention-to-treat. Means of changes in systolic blood pressure values from baseline to 12 weeks between polypill and placebo groups were compared using a 2 sample t-test. Adjusted analyses were carried out by including the stratification factors in an analysis of the covariance regression model with a change in the blood pressure variable as the dependent variable by SAS. The result is p<0.0001.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis was by intention-to-treat. Means of changes in systolic blood pressure values from baseline to 12 weeks between polypill and placebo groups were compared using a 2 sample t-test. Adjusted analyses were carried out by including the stratification factors in an analysis of the covariance regression model with a change in the blood pressure variable as the dependent variable by SAS. The result is p<0.0001.

End point values	Red Heart Pill			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: Hgmm				
number (confidence interval 95%)	-9.9 (-12.1 to -7.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Changes in LDL-cholesterol

End point title	Changes in LDL-cholesterol[3][4]
End point description:	
Intention-to-treat analyses.	

End point type	Primary

End point timeframe:

12 weeks

Notes:

[3] - 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: The primary analysis was by intention-to-treat. Means of changes in LDL-cholesterol values from baseline to 12 weeks between polypill and placebo groups were compared using a 2 sample t-test. Adjusted analyses were carried out by including the stratification factors in an analysis of the covariance regression model with a change in the lipid variable as the dependent variable by SAS. The result is p<0.0001.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis was by intention-to-treat. Means of changes in LDL-cholesterol values from baseline to 12 weeks between polypill and placebo groups were compared using a 2 sample t-test. Adjusted analyses were carried out by including the stratification factors in an analysis of the covariance regression model with a change in the lipid variable as the dependent variable by SAS. The result is p<0.0001.

End point values	Red Heart Pill			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: mm Hg				
number (confidence interval 95%)	-0.8 (-0.9 to -0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Diastolic blood pressure

End point title	Changes in Diastolic blood pressure[5]

End point description:

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis was by intention-to-treat. Means of changes in diastolic blood pressure values from baseline to 12 weeks between polypill and placebo groups were compared using a 2 sample t-test. Adjusted analyses were carried out by including the stratification factors in an analysis of the covariance regression model with a change in the blood pressure variable as the dependent variable by SAS. The result is p<0.0001.

End point values	Red Heart Pill			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: mm Hg				
number (confidence interval 95%)	-5.3 (-6.7 to -3.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Total cholesterol

End point title	Changes in Total cholesterol[6]

End point description:

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis was by intention-to-treat. Means of changes in total cholesterol values from baseline to 12 weeks between polypill and placebo groups were compared using a 2 sample t-test. Adjusted analyses were carried out by including the stratification factors in an analysis of the covariance regression model with a change in the lipid variable as the dependent variable by SAS. The result is $p<0.0001$.

End point values	Red Heart Pill			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: mm Hg				
number (confidence interval 95%)	-0.8 (-1.0 to -0.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Red Heart Pill
Reporting group description:	
Participants received Red Heart Pill (RHP, a polypill comprising a bilayered tablet containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg) for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo	

Serious adverse events	Red Heart Pill	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 189 (2.12%)	4 / 189 (2.12%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 189 (0.53%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Syncope			
subjects affected / exposed	1 / 189 (0.53%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	1 / 189 (0.53%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Ischaemic attack transient			
subjects affected / exposed	0 / 189 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Depression			
subjects affected / exposed	0 / 189 (0.00%)	1 / 189 (0.53%)	
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			
subjects affected / exposed	1 / 189 (0.53%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hip fracture			
subjects affected / exposed	0 / 189 (0.00%)	1 / 189 (0.53%)	
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	Red Heart Pill	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 189 (60.85%)	80 / 189 (42.33%)	
Blood and lymphatic system disorders			
Increased bleed tendency			
subjects affected / exposed	4 / 189 (2.12%)	1 / 189 (0.53%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Dizziness			
subjects affected / exposed	35 / 189 (18.52%)	10 / 189 (5.29%)	
occurrences (all)	35	10	
Headache			

subjects affected / exposed	5 / 189 (2.65%)	3 / 189 (1.59%)	
occurrences (all)	5	3	
Fatigue			
subjects affected / exposed	16 / 189 (8.47%)	12 / 189 (6.35%)	
occurrences (all)	16	12	
Abdominal pain			
subjects affected / exposed	4 / 189 (2.12%)	1 / 189 (0.53%)	
occurrences (all)	4	1	
Other side effect			
subjects affected / exposed	52 / 189 (27.51%)	40 / 189 (21.16%)	
occurrences (all)	52	40	
Gastrointestinal disorders			
Gastric irritation			
subjects affected / exposed	29 / 189 (15.34%)	7 / 189 (3.70%)	
occurrences (all)	29	7	
Diarrhoea			
subjects affected / exposed	4 / 189 (2.12%)	5 / 189 (2.65%)	
occurrences (all)	4	5	
Constipation			
subjects affected / exposed	10 / 189 (5.29%)	4 / 189 (2.12%)	
occurrences (all)	10	4	
Flatulence			
subjects affected / exposed	6 / 189 (3.17%)	5 / 189 (2.65%)	
occurrences (all)	6	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 189 (11.64%)	5 / 189 (2.65%)	
occurrences (all)	22	5	
Musculoskeletal and connective tissue disorders			
Muscle pain			
subjects affected / exposed	14 / 189 (7.41%)	16 / 189 (8.47%)	
occurrences (all)	14	16	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/21647425