Clinical trial results:
UMPIRE - Use of a Multidrug Pill In Reducing cv Events - a randomised controlled trial of fixed dose combination medication and usual care in those at high risk of cardiovascular disease.

Summary

EudraCT number	2009-016278-34
Trial protocol	IE GB NL
Global end of trial date	31 July 2012

Results information

Result version number	v1 (current)
This version publication date	14 May 2020
First version publication date	14 May 2020

Trial information

Trial identification

Sponsor protocol code	241849

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01057537
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	Simon Thom, Imperial College London, s.thom@imperial.ac.uk
Scientific contact	Simon Thom, Imperial College London, 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	31 July 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2012
Global end of trial reached?	Yes
Global end of trial date	31 July 2012
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 assess whether a treatment strategy based on a cardiovascular 'polypill' (a multi-drug pill containing a fixed dose combination of 4 cardiovascular medications) compared to usual cardiovascular medications (similar medications but taken as single tablets) will improve adherence to prescribed medications (i.e. the patient is taking the medications they have been prescribed correctly). Difference in blood pressure and cholesterol between the beginning and end of the trial will serve as indicators of adherence to medication.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2010
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: 335
Country: Number of subjects enrolled	United Kingdom: 336
Country: Number of subjects enrolled	Ireland: 333
Country: Number of subjects enrolled	India: 1000
Worldwide total number of subjects	2004
EEA total number of subjects	1004

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)	1179
From 65 to 84 years	815
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Participants in Europe were recruited via research databases, hospital clinics, and general practice registries at 3 trial centers in London, England; Dublin, Ireland; and Utrecht, the Netherlands. Indian participants were recruited via hospital specialist clinics in 28 centers across the country.

Pre-assignment

Screening details:

A total of 2138 potential participants were screened, 134 were ineligible and 2004 were randomized (1000 in India and 1004 in Europe) between July 2010 and July 2011.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fixed-Dose Combination (FDC)

Arm description:

Participants received either version 1 of 2 FDC formulations chosen by the trial physician: version 1 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and atenolol, 50 mg) or version 2 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and hydrochlorothiazide, 12.5 mg).

Arm type	Experimental
Investigational medicinal product name	FDC Formulation 1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

FDC Formulation 1 (Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg and Atenolol 50 mg). The FDC was taken once daily.

Investigational medicinal product name	FDC Formulation 2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

FDC Formulation 2 (Aspirin 75 mg, Simvastatin 40 mg, Lisinopril 10 mg, and Hydrochlorothiazide 12.5 mg). The FDC was taken once daily.

Arm title	Usual Care

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Usual Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Usual Care

Number of subjects in period 1	Fixed-Dose Combination (FDC)	Usual Care
Started	1002	1002
Completed	955	952
Not completed	47	50
Adverse event, serious fatal	17	15
Consent withdrawn by subject	26	28
Other	4	7

Baseline characteristics

Reporting groups	
Reporting group title	Fixed-Dose Combination (FDC)
Reporting group description:	
Participants received either version 1 of 2 FDC formulations chosen by the trial physician: version 1 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and atenolol, 50 mg) or version 2 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and hydrochlorothiazide, 12.5 mg).	
Reporting group title	Usual Care
Reporting group description: -	

Reporting group values	Fixed-Dose Combination (FDC)	Usual Care	Total
Number of subjects	1002	1002	2004
Age categorical Units: Subjects			
Adults (18-74)	1002	1002	2004
Age continuous Units: years			
arithmetic mean	62.1	61.6	
standard deviation	± 10.4	± 10.8	-
Gender categorical Units: Subjects			
Female	185	177	362
Male	817	825	1642
Systolic Blood Pressure Units: mm Hg			
arithmetic mean	137	137.7	
standard deviation	± 21.3	± 21.1	-
Diastolic Blood Pressure Units: mm Hg			
arithmetic mean	77.4	78.1	
standard deviation	± 12	± 11.5	-
low-density lipoprotein cholesterol (LDL-C) Units: mg/dL			
arithmetic mean	90.5	92.5	
standard deviation	± 32.5	± 36	-

End points

End points reporting groups

Reporting group title	Fixed-Dose Combination (FDC)
Reporting group description:	
Participants received either version 1 of 2 FDC formulations chosen by the trial physician: version 1 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and atenolol, 50 mg) or version 2 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and hydrochlorothiazide, 12.5 mg).	
Reporting group title	Usual Care
Reporting group description: -	

Primary: Adherence to medication

End point title	Adherence to medication
End point description:	
Number of participants who adhere to the medication	
End point type	Primary
End point timeframe:	
18 months	

End point values	Fixed-Dose Combination (FDC)	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	961	960		
Units: Number of participants	829	621		

Statistical analyses

Statistical analysis title	Adherence
Statistical analysis description:	
Relative risks (RRs) of self-reported adherence to indicated medications at the end of the study were calculated using log-binomial regression including randomized treatment. Adjusted analyses included randomized treatment, baseline value (either SBP, LDL-C, or baseline adherence) plus age, sex, country, and established disease as covariates.	
Comparison groups	Fixed-Dose Combination (FDC) v Usual Care
Number of subjects included in analysis	1921
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Relative Risk
Parameter estimate	Log-binomal regression
Point estimate	1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	1.41

Primary: Systolic Blood Pressure

End point title	Systolic Blood Pressure

End point description:

End point type	Primary

End point timeframe:

18 months

End point values	Fixed-Dose Combination (FDC)	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	961	960		
Units: mm Hg				
arithmetic mean (full range (min-max))	129.2 (128.1 to 130.2)	131.7 (130.7 to 132.8)		

Statistical analyses

Statistical analysis title	Systolic Blood Pressure

Statistical analysis description:

The primary analysis of mean differences in changes in SBP at the end of study between the FDC and usual care groups was conducted using analysis of covariance including the randomized treatment and baseline SBP. Longitudinal analyses using generalized linear models with a compound-symmetry covariance structure were used as sensitivity analyses for the 3 primary end points.

Comparison groups	Fixed-Dose Combination (FDC) v Usual Care
Number of subjects included in analysis	1921
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	log-binomial regression
Parameter estimate	Log-binomal regression
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	-1.1

Notes:

[1] - Adjusted analyses included randomized treatment, baseline value plus age, sex, country, and established disease as covariates.

Primary: Low-density lipoprotein cholesterol

End point title	Low-density lipoprotein cholesterol

End point description:

End point type	Primary

End point timeframe:

18 months

End point values	Fixed-Dose Combination (FDC)	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	961	960		
Units: mg/dL				
arithmetic mean (full range (min-max))	84.2 (82.5 to 85.8)	88.4 (86.7 to 90)		

Statistical analyses

Statistical analysis title	Low-density lipoprotein cholesterol

Statistical analysis description:

The primary analysis of mean differences in changes in LDL-C at the end of study between the FDC and usual care groups was conducted using analysis of covariance including the randomized treatment and baseline LDL-C.

Comparison groups	Fixed-Dose Combination (FDC) v Usual Care
Number of subjects included in analysis	1921
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	log-binomial regression
Parameter estimate	Log-binomal regression
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	-1.9

Notes:

[2] - Adjusted analyses included randomized treatment, baseline value plus age, sex, country, and established disease as covariates.

Secondary: Diastolic Blood Pressure

End point title	Diastolic Blood Pressure

End point description:

End point type	Secondary
End point timeframe: 18 months	

End point values	Fixed-Dose Combination (FDC)	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	961	960		
Units: mm Hg				
arithmetic mean (full range (min-max))	72.8 (72.2 to 73.5)	75.2 (74.7 to 75.8)		

Statistical analyses

Statistical analysis title	Diastolic Blood Pressure
Statistical analysis description: Continuous secondary end points including diastolic BP were assessed using analysis of covariance.	
Comparison groups	Fixed-Dose Combination (FDC) v Usual Care
Number of subjects included in analysis	1921
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Log-binomial regression
Parameter estimate	log-binomial regression
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-1.6

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

18 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Fixed-Dose Combination (FDC)

Reporting group description:

Participants received either version 1 of 2 FDC formulations chosen by the trial physician: version 1 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and atenolol, 50 mg) or version 2 (aspirin, 75 mg; simvastatin, 40 mg; lisinopril, 10 mg; and hydrochlorothiazide, 12.5 mg).

Reporting group title	Usual Care

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: This is correct as reported.

Serious adverse events	Fixed-Dose Combination (FDC)	Usual Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	118 / 1002 (11.78%)	102 / 1002 (10.18%)	
number of deaths (all causes)	17	15	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign and malignant			
subjects affected / exposed	13 / 1002 (1.30%)	11 / 1002 (1.10%)	
occurrences causally related to treatment / all	0 / 13	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	11 / 1002 (1.10%)	12 / 1002 (1.20%)	
occurrences causally related to treatment / all	0 / 11	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed[2]	3 / 961 (0.31%)	2 / 960 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed[3]	8 / 961 (0.83%)	8 / 960 (0.83%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorders			
subjects affected / exposed[4]	0 / 961 (0.00%)	1 / 960 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed[5]	1 / 961 (0.10%)	6 / 960 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed[6]	5 / 961 (0.52%)	3 / 960 (0.31%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed[7]	1 / 961 (0.10%)	2 / 960 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations			
subjects affected / exposed[8]	1 / 961 (0.10%)	0 / 960 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			

subjects affected / exposed[9]	7 / 961 (0.73%)	5 / 960 (0.52%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders			
subjects affected / exposed[10]	0 / 961 (0.00%)	1 / 960 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	42 / 1002 (4.19%)	27 / 1002 (2.69%)	
occurrences causally related to treatment / all	0 / 42	0 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	9 / 1002 (0.90%)	13 / 1002 (1.30%)	
occurrences causally related to treatment / all	0 / 9	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed[11]	1 / 961 (0.10%)	0 / 960 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	10 / 1002 (1.00%)	11 / 1002 (1.10%)	
occurrences causally related to treatment / all	0 / 10	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed[12]	1 / 961 (0.10%)	1 / 960 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Skin and subcutaneous tissue disorders			
subjects affected / exposed[13]	0 / 961 (0.00%)	1 / 960 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed[14]	5 / 961 (0.52%)	3 / 960 (0.31%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed[15]	3 / 961 (0.31%)	6 / 960 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	16 / 1002 (1.60%)	10 / 1002 (1.00%)	
occurrences causally related to treatment / all	0 / 16	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed[16]	3 / 961 (0.31%)	5 / 960 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

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Justification: This is correct as reported.

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Justification: This is correct as reported.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is correct as reported.

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

Non-serious adverse events	Fixed-Dose Combination (FDC)	Usual Care	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 1002 (0.00%)	0 / 1002 (0.00%)	

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/24002278