Clinical trial results:
Secondary Prevention of Cardiovascular Disease in the Elderly Trial (SECURE)

Summary

EudraCT number	2015-002868-17
Trial protocol	DE ES CZ HU IT
Global end of trial date	31 March 2022

Results information

Result version number	v1 (current)
This version publication date	18 August 2024
First version publication date	18 August 2024
Summary attachment (see zip file)	Synopsis (Synopsis SECURE Trial EudraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	633765

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02596126
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centro Nacional de Investigaciones Cardiovasculares, Carlos III (CNIC) (FSP)
Sponsor organisation address	C/ Melchor Fernandez Almagro 3, Madrid, Spain, 28029
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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	10 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a polypill strategy containing aspirin (100 mg), ramipril (2.5, 5 or 10 mgs), and atorvastatin (40 or 20 mgs) compared with the standard of care (usual care according to the local clinical practices at each participating country) in secondary prevention of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, and urgent revascularization).

Protection of trial subjects:

No relevant safety information has been generated during the trial. Moreover, no safety problems which could present a non-major benefit-risk consideration were presented during the trial so that the PVG department did not see any reason to take any different or special safety measure or even considering the premature discontinuation of this study.

Background therapy:

The main aim of SECURE is to evaluate the efficacy of a polypill strategy containing aspirin (100 mg), ramipril (2.5, 5 or 10 mgs), and atorvastatin (40 or 20 mgs) compared with the standard of care (usual care according to the local clinical practices at each participating country) in secondary prevention of major cardiovascular events.

Evidence for comparator: -

Actual start date of recruitment	06 May 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 124
Country: Number of subjects enrolled	Spain: 859
Country: Number of subjects enrolled	Czechia: 174
Country: Number of subjects enrolled	France: 144
Country: Number of subjects enrolled	Germany: 372
Country: Number of subjects enrolled	Hungary: 92
Country: Number of subjects enrolled	Italy: 734
Worldwide total number of subjects	2499
EEA total number of subjects	2499

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)	0
From 65 to 84 years	2499
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients will be recruited across seven countries in Europe (Spain, Italy, Germany, France, Hungary, Poland, and Czech Republic). Patients were ≥65 years old and diagnosed with a type 1 myocardial infarction within 6 months prior to study enrolment.

Pre-assignment

Screening details:

Patients can be screened at any time within the first 8 weeks after index event (type 1 myocardial infarction) whenever they are clinically stable and ready to receive secondary prevention therapy, including the hospital phase. Patients with ventricular arrhythmias needing further evaluation of therapy.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

DESIGN: Multicenter, open-label, randomized, open-label, repeated-dose, adaptive parallel two arms trial, as we are comparing the pollypil with the standard of care by jugment of the physician

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard of Care

Arm description:

Standard of care for secondary prevention carried out according to current ESC clinical guidelines

Arm type	Standard of Care
Investigational medicinal product name	Ramipril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

according to current ESC clinical guidelines.

Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

according to current ESC clinical guidelines.

Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

according to current ESC clinical guidelines.

Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: according to current ESC clinical guidelines.	
Investigational medicinal product name	Pravastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: according to current ESC clinical guidelines.	
Investigational medicinal product name	Lovastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: according to current ESC clinical guidelines.	
Investigational medicinal product name	Pitavastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: according to current ESC clinical guidelines.	
Investigational medicinal product name	Fluvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: according to current ESC clinical guidelines.	
Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: according to current ESC clinical guidelines.	
Investigational medicinal product name	Perindopril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use
Dosage and administration details: according to current ESC clinical guidelines.	
Investigational medicinal product name	Lisinopril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

according to current ESC clinical guidelines.

Arm title	Intervention Arm

Arm description:

Patients randomized to Cardiovascular Combination Pill AAR ASA 100 mg, Atorvastatin (40) mg, Ramipril 2.5 / 5 / 10) mg.
If considered necessary and per investigators' judgment, the Cardiovascular Combination Polypill AAR 40 may be switched to Cardiovascular Combination Polypill AAR 20 (Atorvastatin 20 mg, ASA 100mg and Ramipril 2.5, 5 or 10 mg)

Arm type	Experimental
Investigational medicinal product name	Acetylsalicylic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg daily

Investigational medicinal product name	Ramipril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 / 5 / 10 mg according to physician's criteria

Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

20 / 40 mg according to physician's criteria

Number of subjects in period 1	Standard of Care	Intervention Arm
Started	1241	1258
Completed	1222	1228
Not completed	19	30
Lost to follow-up	12	21
Protocol deviation	7	9

Baseline characteristics

Reporting groups

Reporting group title	Standard of Care

Reporting group description:

Standard of care for secondary prevention carried out according to current ESC clinical guidelines

Reporting group title	Intervention Arm

Reporting group description:

Patients randomized to Cardiovascular Combination Pill AAR ASA 100 mg, Atorvastatin (40) mg, Ramipril 2.5 / 5 / 10) mg.
If considered necessary and per investigators' judgment, the Cardiovascular Combination Polypill AAR 40 may be switched to Cardiovascular Combination Polypill AAR 20 (Atorvastatin 20 mg, ASA 100mg and Ramipril 2.5, 5 or 10 mg)

Reporting group values	Standard of Care	Intervention Arm	Total
Number of subjects	1241	1258	2499
Age categorical Units: Subjects			
From 65-84 years	1241	1258	2499
Gender categorical Units: Subjects			
Female	383	392	775
Male	858	866	1724

Subject analysis sets

Subject analysis set title	ITT comparison
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients, analysed according to the group to which they were randomised. This will be the population for the primary analysis.

Subject analysis set title	PP Population analysis
Subject analysis set type	Per protocol

Subject analysis set description:

All randomised patients who received at least one dose of IMP, and have no major protocol deviations, analysed according to the group to which they were randomised. Patients with major protocol deviations will be identified before database lock and unblinding.

Reporting group values	ITT comparison	PP Population analysis	
Number of subjects	2466	2450	
Age categorical Units: Subjects			
From 65-84 years	2466	2450	
Gender categorical Units: Subjects			
Female	765	757	
Male	1701	1693	

End points

End points reporting groups

Reporting group title	Standard of Care

Reporting group description:

Standard of care for secondary prevention carried out according to current ESC clinical guidelines

Reporting group title	Intervention Arm

Reporting group description:

Patients randomized to Cardiovascular Combination Pill AAR ASA 100 mg, Atorvastatin (40) mg, Ramipril 2.5 / 5 / 10) mg.
If considered necessary and per investigators' judgment, the Cardiovascular Combination Polypill AAR 40 may be switched to Cardiovascular Combination Polypill AAR 20 (Atorvastatin 20 mg, ASA 100mg and Ramipril 2.5, 5 or 10 mg)

Subject analysis set title	ITT comparison
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Subject analysis set description:

All randomised patients, analysed according to the group to which they were randomised. This will be the population for the primary analysis.

Subject analysis set title	PP Population analysis
Subject analysis set type	Per protocol

Subject analysis set description:

All randomised patients who received at least one dose of IMP, and have no major protocol deviations, analysed according to the group to which they were randomised. Patients with major protocol deviations will be identified before database lock and unblinding.

Primary: Major Cardiovascular Adverse Events (MACE)

End point title	Major Cardiovascular Adverse Events (MACE)

End point description:

The incidence of the first occurrence of any component of the following composite endpoint, as adjudicated by the Clinical Events Committee:
- Cardiovascular death.
- Any nonfatal type 1 myocardial infarction.
- Any nonfatal ischemic stroke.
- Any urgent coronary revascularization not resulting in death.

End point type	Primary

End point timeframe:

After randomization during the trial, first occurence

End point values	Standard of Care	Intervention Arm	ITT comparison	PP Population analysis
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	1241[1]	1258[2]	2466[3]	2450[4]
Units: number of adjudicated events	156	118	274	272

Notes:

[1] - Stardard of Care

[2] - ITT poluplation

[3] - Total population included in the ITT analysis

[4] - number of participants included in the PP analysis

Statistical analyses

Statistical analysis title	Non-inferiority test

Statistical analysis description:

Non-inferiority hypotheshis will be tested using a univariable Cox PH regression model including treatment group as the only covariate and stratified by country.

Comparison groups	Intervention Arm v Standard of Care
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.025 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.96

Notes:

[5] - One-sided non-inferiority test on the primary endpoint where the alpha level will be set to 2.5%. All statistical analyses will use 95% confidence intervals (CI). If the non-inferiority hypothesis is confirmed, it will be followed with a test of superiority using a log-rank test.
[6] - One-sided test

Statistical analysis title	Superiority test

Statistical analysis description:

If the non-inferiority hypothesis is confirmed, it will be followed with a test of superiority using a log-rank test.

Comparison groups	Standard of Care v Intervention Arm
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.05
Method	Logrank

Notes:

[7] - Test of superiority using a log-rank test.

Secondary: Efficacy endpoints

End point title	Efficacy endpoints

End point description:

a. The first occurrence of any component of the following composite endpoint: CV death, MI type 1, stroke.
b. The first occurrence of the individual components of the primary endpoint
- CV death.
- Nonfatal type 1 myocardial infarction.
- Nonfatal ischemic stroke.
- Urgent coronary revascularization.
c. Improvement in treatment adherence at 2 years, as measured by Morisky Medication Adherence Scale (MMAS-8).
d. Change of risk factor control at 2 years
- LDL-cholesterol level.
- SBP.
- DBP.
e. Cost effectiveness of the polypill strategy.
f. Performance of the polypill strategy across different socioeconomic and health settings.
g. Treatment Satisfaction.

End point type	Secondary

End point timeframe:

Anytime after the randomization

End point values	Standard of Care	Intervention Arm	ITT comparison	PP Population analysis
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	1241	1258	2466	2450
Units: number of events	1057	1077	1057	1077

Statistical analyses

Statistical analysis title	Treatment adherence at 6 months

Statistical analysis description:

Treatment adherence is measured at visit 1 (6 months) and visit 3 (24 months) using the Morisky-Medication Adherence Scale (8 item) Questionnaire (MMAS-8). The number and percentage of patients with low (0-5), medium (6-7) and high (8) adherence will be reported by treatment group. The distributions of the MMAS-8 score at 6 months and 24 months will be compared between treatment groups using an ordinal logistic regression model.

Comparison groups	Standard of Care v Intervention Arm
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.005
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.2

Statistical analysis title	Treatment adherence at 24 months

Statistical analysis description:

Treatment adherence is measured at visit 1 (6 months) and visit 3 (24 months) using the Morisky-Medication Adherence Scale (8 item) Questionnaire (MMAS-8). The number and percentage of patients with low (0-5), medium (6-7) and high (8) adherence will be reported by treatment group. The distributions of the MMAS-8 score at 6 months and 24 months will be compared between treatment groups using an ordinal logistic regression model.

Comparison groups	Standard of Care v Intervention Arm

Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.005
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.25

Statistical analysis title	SBP - 6 months

Statistical analysis description:

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from baseline between groups will be compared using ANCOVA.

Comparison groups	Standard of Care v Intervention Arm
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.2

Notes:

[8] - The difference in mean change from baseline between groups will be compared using ANCOVA (adjusting for baseline levels) at 6 months, 12 months and 24 months. The difference in mean change adjusting for baseline and 95% CI will be reported.

Statistical analysis title	SBP - 12 months

Statistical analysis description:

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from baseline between groups will be compared using ANCOVA.

Comparison groups	Standard of Care v Intervention Arm

Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [9]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	3

Notes:

[9] - The difference in mean change from baseline between groups will be compared using ANCOVA (adjusting for baseline levels) at 6 months, 12 months and 24 months. The difference in mean change adjusting for baseline and 95% CI will be reported.

Statistical analysis title	SBP - 24 months

Statistical analysis description:

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from baseline between groups will be compared using ANCOVA.

Comparison groups	Standard of Care v Intervention Arm
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence[10]
P-value	< 0.05 [11]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	1.4

Notes:

[10] - The difference in mean change from baseline between groups will be compared using ANCOVA (adjusting for baseline levels) at 6 months, 12 months and 24 months. The difference in mean change adjusting for baseline and 95% CI will be reported.

[11] - The difference in mean change from baseline between groups will be compared using ANCOVA (adjusting for baseline levels) at 6 months, 12 months and 24 months. The difference in mean change adjusting for baseline and 95% CI will be reported.

Statistical analysis title	DBP - 6 months

Statistical analysis description:

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from baseline between groups will be compared using ANCOVA.

Comparison groups	Standard of Care v Intervention Arm

Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [12]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1

Notes:

[12] - The difference in mean change from baseline between groups will be compared using ANCOVA (adjusting for baseline levels) at 6 months, 12 months and 24 months. The difference in mean change adjusting for baseline and 95% CI will be reported.

Statistical analysis title	DBP - 12 months

Statistical analysis description:

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from baseline between groups will be compared using ANCOVA.

Comparison groups	Standard of Care v Intervention Arm
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [13]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.6

Notes:

[13] - The difference in mean change from baseline between groups will be compared using ANCOVA (adjusting for baseline levels) at 6 months, 12 months and 24 months. The difference in mean change adjusting for baseline and 95% CI will be reported.

Statistical analysis title	DBP - 24 months

Statistical analysis description:

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from baseline between groups will be compared using ANCOVA.

Comparison groups	Standard of Care v Intervention Arm

Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [14]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1

Notes:

[14] - The difference in mean change from baseline between groups will be compared using ANCOVA (adjusting for baseline levels) at 6 months, 12 months and 24 months. The difference in mean change adjusting for baseline and 95% CI will be reported.

Statistical analysis title	LDL cholesterol - 12 months

Statistical analysis description:

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from baseline between groups will be compared using ANCOVA.

Comparison groups	Standard of Care v Intervention Arm
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	4.4

Statistical analysis title	LDL cholesterol - 24 months

Statistical analysis description:

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from baseline between groups will be compared using ANCOVA.

Comparison groups	Standard of Care v Intervention Arm

Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	2.4

Secondary: Safety endpoints

End point title	Safety endpoints

End point description:

All-cause mortality.
Non-cardiovascular death

End point type	Secondary

End point timeframe:

Anytime after randomization

End point values	Standard of Care	Intervention Arm	ITT comparison	PP Population analysis
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	1241	1258	2466	2450
Units: number of events	326	363	345	344

Statistical analyses

Statistical analysis title	All-cause death

Statistical analysis description:

Time to first event will be investigated using Cox proportional hazards regression. Hazard ratios and 95% confidence intervals will be obtained from the Cox proportional hazards model. P-values will be obtained using the log-rank test.

Comparison groups	Standard of Care v Intervention Arm
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.25

Statistical analysis title	Non-cardiovascular death

Statistical analysis description:

Time to first event will be investigated using Cox proportional hazards regression. Hazard ratios and 95% confidence intervals will be obtained from the Cox proportional hazards model. P-values will be obtained using the log-rank test.

Comparison groups	Standard of Care v Intervention Arm
Number of subjects included in analysis	2499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.07

Adverse events

Adverse events information

Timeframe for reporting adverse events:

yearly after first patient

Adverse event reporting additional description:

Aspirin, Atorvastatin, and Ramipril have been extensively studied in Phase 1 through Phase 4 clinical studies and their overall safety profile has been well characterized. Thus, appropriate information concerning adverse events were systematically collected and submitted to regulatory authorities

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Standard of Care

Reporting group description:

Adverse Events are classified by body system according to MedDRA English V 4.0.0.97. Adverse events are displayed in absolute data and rate (%) of adverse events. In addition, adverse events are classified according to the study period (screening phase, treatment phase) and itemized by severity and relationship.
The following adverse events or serious adverse events were collected and entered into the eCRF:
• Adverse events leading to change of dose or permanent study drug discontinuation
• All drug related adverse event: ADR, SADR and SUSAR
• Bleeding: according to Bleeding Academic Research Consortium Definition
• Renal dysfunction
• Angioedema

Reporting group title	Intervention Arm

Reporting group description: -

Serious adverse events	Standard of Care	Intervention Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	224 / 1229 (18.23%)	237 / 1237 (19.16%)	
number of deaths (all causes)	117	115	
number of deaths resulting from adverse events			
Cardiac disorders			
Non fatal SAEs			
subjects affected / exposed	224 / 1229 (18.23%)	237 / 1237 (19.16%)	
occurrences causally related to treatment / all	45 / 346	41 / 339	
deaths causally related to treatment / all	0 / 117	0 / 115	

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

Non-serious adverse events	Standard of Care	Intervention Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	388 / 1229 (31.57%)	404 / 1237 (32.66%)	
Cardiac disorders			
BARC bleeding			
subjects affected / exposed	49 / 1229 (3.99%)	57 / 1237 (4.61%)	
occurrences (all)	49	57	
Refractory cough			
subjects affected / exposed	35 / 1229 (2.85%)	40 / 1237 (3.23%)	
occurrences (all)	35	40	
Drug Allergy			
subjects affected / exposed	7 / 1229 (0.57%)	14 / 1237 (1.13%)	
occurrences (all)	7	14	
AEs of no interest			
subjects affected / exposed	275 / 1229 (22.38%)	269 / 1237 (21.75%)	
occurrences (all)	275	269	
Renal and urinary disorders			
Renal			
subjects affected / exposed	22 / 1229 (1.79%)	24 / 1237 (1.94%)	
occurrences (all)	22	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2016	- Added new exclusion criterion: "2. Inability to understand and comply with the protocol requirements and instructions." - Section 4.3 and 4.4: Updated members of CEC and DSMB. - Section 7.8, 7.9, 7.11, and 8.6: Updated criteria - Section 8.3.1: Added specification of drug supply for Germany - Section 8.6: Added treatment compliance and missed dose procedure under 8.6.1. - Section 8.10.1: Updated definition of Resource Use and Costs - Section 9: patient follow-up for Germany and removed collection of Hb1Ac. - Section 10.2.4.1: Added "Definitely Related" to Assessment of Causality. - Annex 1: Name of Béla Merkely added for Hungary. - Annex 3: Definition of MI. - Annex 8: Corrected MMAS-8's score assessment of question 5 and 8. - Annex 13: Helsinki 1996 version was added. - Annex 14: Added Withdrawal of Consent Checklist
01 July 2017	- Section 1.1: Visiting Schema updated to reflect protocol changes on data collection and inclusion criteria (time of MI increased) - Section 5, 6.1,7.2, 7.3, and 7.6: Inclusion Criteria on time of MI increased from 8 weeks to 6 months - Section 7.7: Clarified information on safety assessment and patient follow-up - Section 7.8-7.10: Reorganized, clarified, and condensed withdrawal of patient from treatment and trial discontinuation - Section 7.11: New section added to address patient follow up after site closure - Section 8.1: Updated storage conditions and added relabeling information - Section 8.3: Updated drug supply section to clarify dispensation - Section 9.1: Removed MMAS-8 from baseline, and transferred TSQM questionnaire from Baseline to six (6) month visit - Section 13.3.2. and 11.4.2: Health Economic Endpoints were further specified and definition of the data/variables to be collected were included - Section 10.3.4: Edited and updated the list of reportable Adverse Events - Annex 13.2: Helsinki 2013 version was added per the request of Hungarian authorities - Updated Investigators brochure to V4
01 October 2018	- Updated of Investigator's brochure V5 and V6
07 October 2019	- Change in the target number of patients from 3206 to 2514 with updated statistical analysis (different sections through the protocol). - Section 1.1 Visiting Schema. Updated schema including 60 months follow-up by telephone call. - Section 1.2 Study Flow chart including 60 months follow-up by telephone call. - Section 4.3 Data Safety and Monitoring Board update. - Section 4.4 Clinical Events Committee update. - Section 8.1 IMP Drug Supply - New Section 9.1.8 with telephone Follow-up 4. - Section 11.6.1 Determination of Sample Size. Updated calculations. - Annex 1: Participating Organization. Updated information of CNIC. - Updated informed consent - Updated Investigator's brochure to V7

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although SECURE was not a blinded trial, the event adjudicators were blinded and endpoint assessment was unbiased. No adjustment was made for multiple comparisons of secondary endpoints

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36018037