2.SYNOPSIS

Name of Sponsor/Company: Fundación Centro Nacional de Investigaciones Cardiovasculares, Carlos III (CNIC)
Name of Finished Product: TRINOMIA
Name of Active Ingredient: acetysalicylic acid 100 mg, atorvastin 40 mg or 20 mg, and ramipril 10, 5 and 2.5 mg
Title of Study: Secondary Prevention of Cardiovascular Disease in the Elderly Trial (SECURE)
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Studied period (years): 5 years & 8 months **(date of first enrolment):** 8 August 2016 **(date of last completed):** 31 October 2021	**Phase of development:** Phase III

Objectives:

Primary Objective

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).

The **secondary objectives** are to evaluate a polypill strategy as compared with standard of care for secondary cardiovascular prevention after MI in an elderly population in:

- reducing other clinical endpoints.
- improving baseline adherence.
- improving quality of life.
- controlling cardiovascular risk factors. (LDL cholesterol, systolic and diastolic blood pressure).
- Cost-effectiveness
- safety and tolerability
- patient satisfaction

performance across the different socioeconomic and health settings.

Methodology: SECURE is a randomized, un-blinded, controlled, 2-group, parallel, multinational trial which includes 2499 patients over 65 post MI from Spain, Italy, France, Germany, Poland, Czech Republic and Hungary. The primary end point is to assess the efficacy of a polypill (including aspirin[100mg], Ramipril [2.5-5-10mgs], atorvastatin [20-40mgs] – a total of six different formulations) with taking several drugs separately (usual

care according to the local clinical practices at each participating country) in secondary prevention of cardiovascular events (incidence of the first occurrence of any component of the following composite endpoint, as adjudicated by the Clinical Events Committee: death from cardiovascular causes, nonfatal myocardial infarction, stroke, and urgent revascularization not resulting in death). The median follow up has been 36 months.
All patients were included in the study and randomized after signing informed consent at the time of the event. Patients randomized to the polypill arm received the polypill freely by the study. Patients randomised to polypill arm began treatment at the discretion of the physician, within 7 days of the index event (or at discharge for patients requiring longer hospitalisations). Patients randomized to the control group received usual care.
The minimun FU was 24 months. The patients underwent 3 presential visits (6mo, 12mo and 24mo) and up to 4 telephone FU calls (18mo, 36mo, 48mo and 60mo)

Number of patients (planned and analyzed): 2514 patients planned, finally 2499 randomized patients

Diagnosis and main criteria for inclusion:

1. Giving consent after information.
2. Patients diagnosed with a type 1 myocardial infarction within the previous 6 months.
3. Subjects must be ≥65 years old, presenting with **at least one** of the following additional conditions:
    i. Documented diabetes mellitus or previous treatment with oral hypoglycemic drugs or insulin.
    ii. Mild to moderate renal dysfunction: creatinine clearance 60-30 mL/min/1.73 m^2.
    iii. Prior myocardial infarction: defined as an AMI occurring before the index event documented in a medical report.
    iv. Prior coronary revascularization: coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).
    v. Prior stroke: history of a documented stroke, defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue, not resulting in death.
    vi. Age ≥ 75 years.

Test product, dose and mode of administration:
ATC:
Patients randomized to Cardiovascular Combination Pill AAR arm will receive one of the following treatments:

Cardiovascular Combination Polypill AAR 40

ASA 100 mg, Atorvastatin 40 mg, Ramipril 2.5mg

ASA 100 mg, Atorvastatin 40 mg, Ramipril 5 mg

ASA 100 mg, Atorvastatin 40 mg, Ramipril 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)

Intervention Arm: once daily administration of one capsule (Cardiovascular Combination Polypill AAR).

Usual Care: Standard of care for secondary prevention will be carried out according to current ESC clinical guidelines.

Oral Administration

Duration of treatment: Physician Criteria

Criteria for evaluation:

Primary Endpoint

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.

Secondary Endpoints

1. Efficacy endpoints
   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.

2. Safety endpoints
   a. All-cause mortality.
   b. Adverse Events
      i. Bleeding
      ii. Renal dysfunction.
      iii. Drug allergic reaction.

iv. Refractory cough leading to drug discontinuation.
v. Drug Discontinuation.

Efficacy:

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. The hypothesis of SECURE is that the use of a polypill strategy including three components with proven efficacy as well as demonstrated positive impact on adherence will reduce major cardiovascular events in patients with myocardial infarction (MI) by reducing treatment complexity, lack of adherence and achieving better risk factor control, reducing the risk of recurrent disease and death in elderly patients with CVD, and thereby reducing the burden of CVD in Europe.

Safety:

Secondary safety outcomes included death from any cause and adverse events (including bleeding, kidney failure, drug allergic reaction, and drug discontinuation). Sensitivity analyses were also performed to consider noncardiovascular death as a competing risk for the primary outcome and key secondary outcome.

Statistical methods:
The planned total sample size in this study is 2514 patients (1257 per group). The initial assumptions for the determination of sample size are as following:

- A composite primary endpoint event rate of 7.7% per year in the population to be recruited
- A true hazard ratio of 1
- A planned accrual period for the study of 3 years
- A minimum follow-up and treatment period of 2 years
- An estimated loss to follow-up of 1%

Based on these assumptions, it is anticipated that 420 composite primary events will be accrued during the follow-up period. A non-inferiority margin of 1.373 for the upper limit of the 95% confidence interval for the hazard ratio is set for this study. With the total sample size of 2514 patients (1257 per group) a noninferiority test at 0.025 one-sided significance level with have a 90% power to reject the null hypothesis of inferiority.

With this sample size, the study will have 78% power at a two-sided alpha of 0.05 to demonstrate a relative risk reduction of 21%, which corresponds to a hazard ratio 0.79.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:
A total of 2499 patients underwent randomization and were followed for a median

of 36 months. A primary-outcome event occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 (12.7%) in the usual-care group (hazard ratio, 0.76; 95% confidence interval [CI], 0.60 to 0.96; P = 0.02). A key secondaryoutcome event occurred in 101 patients (8.2%) in the polypill group and in 144 (11.7%) in the usual-care group (hazard ratio, 0.70; 95% CI, 0.54 to 0.90; P = 0.005). The results were consistent across prespecified subgroups. Medication adherence as reported by the patients was higher in the polypill group than in the usual-care group. Adverse events were similar between groups.

SAFETY RESULTS:
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.
Adverse events were reported in 404 of 1237 patients (32.7%) in the polypill group and in 388 of 1229 (31.6%) in the usual-care group. Nonfatal serious adverse events occurred in 237 patients (19.2%) in the polypill group and in 224 (18.2%) in the usual-care group.

CONCLUSION:

Treatment with a polypill containing aspirin, ramipril, and atorvastatin within 6 months after myocardial infarction resulted in a significantly lower risk of major adverse cardiovascular events than usual care