Clinical trial results:
A multicentre, randomised, open-label, parallel-group trial to study the safety and efficacy of a new therapeutic strategy (Trinomia®*) versus usual care on LDLc and blood pressure levels in patients with atherothrombotic cardiovascular disease: The APOLO trial.

Summary

EudraCT number	2017-002343-14
Trial protocol	IE ES PT
Global end of trial date	09 March 2021

Results information

Result version number	v1 (current)
This version publication date	27 October 2022
First version publication date	27 October 2022

Trial information

Trial identification

Sponsor protocol code	FMD-TRI-2017-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ferrer Internacional S.A.
Sponsor organisation address	Avinguda Diagonal, 549, Barcelona, Spain, 08029
Public contact	Ferrer, Ferrer Internacional S.A., +34 936 00 37 00, clinicaldevelopment@ferrer.com
Scientific contact	Clinical Development Lead, Ferrer Internacional S.A., +34 662 213 660, raldonza@ferrer.com

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	24 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to determine whether the treatment with a new therapeutic strategy (Trinomia®)) is at least non-inferior to usual care in terms of low-density lipoprotein cholesterol (LDLc) and systolic blood pressure reductions in subjects with atherothrombotic cardiovascular disease after 6 months of treatment.

Protection of trial subjects:

This clinical trial was conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki (Fortaleza, Brazil; October 2013), the Harmonized Tripartite Guidelines for Good Clinical Practice and applicable regulatory requirements.
The study was not started until approval by the ethics committee and other pertinent authorities was obtained. By signing the protocol, the investigator agreed to adhere to the instructions and procedures described in the protocol and therefore to comply the principles of good clinical practice they entail.
Any amendment changing the risk-benefit relationship for the patient was, after signature by the sponsor, submitted for evaluation by the ethics committees and the regulatory authorities for approval. The study investigators were also informed and gave their written approval for the amendment.
Informed consent for participation in the study was freely granted before performing any study-specific procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 192
Country: Number of subjects enrolled	Spain: 252
Country: Number of subjects enrolled	Ireland: 28
Country: Number of subjects enrolled	Ukraine: 83
Worldwide total number of subjects	555
EEA total number of subjects	472

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)	262
From 65 to 84 years	292
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Between June 2018 and March 2021, 555 patients were enrolled in this study. Eleven patients from the Hospital Universitario Virgen del Rocío, 52 from the Hospital Gregorio Marañón, and nine from the Hospital San Juan were excluded because of an inspection and audits. Of the remaining 483 patients, 37 were screening failures and 446 were randomized.

Pre-assignment

Screening details:

Subjects ≥18 with atherothrombotic cardiovascular disease and at least one of them: previous acute myocardial infarction, cardiac revascularization with coronary stent, coronary artery bypass grafting, diagnosis of stable angina, previous ischemic stroke or peripheral artery disease. Excluded for any contraindication to the cardiovascular polypill.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trinomia group

Arm description:

Patients in the Trinomia group incorporated the cardiovascular polypill in their therapeutic strategy. Therefore, patients substituted the angiotensin converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB), statin and acetylsalicylic acid by the cardiovascular polypill. In addition, patients may have taken any other medication that they were taking before.
Replacing the cardiovascular polypill should have been done on the basis that patients were stable and no changes in medication for LDLc and was planned. According to these premises, the doses of atorvastatin (20 or 40 mg) and ramipril (2,5 to 10 mg) were chosen according to the equivalent doses of ARBs/ACEIs and statins that he/she had been taken before entering the study.

Arm type	Experimental
Investigational medicinal product name	Cardiovascular polypill
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Each capsule contains 100 mg of acetylsalicylic acid, 20 mg or 40 mg of atorvastatin and 2.5 mg, 5 mg, or 10 mg of ramipril. Excipients with known effect: 73.61 mg of lactose monohydrate and 0.48 mg of soy lecithin.
Size 0 hard gelatine capsules with opaque pale pink-coloured cap and body (the cardiovascular polypill 100 mg/ 20 or 40 mg/ 10 mg), opaque pale pink-coloured cap and opaque pale grey-coloured body (the cardiovascular polypill 100 mg/ 20 or 40 mg/ 5 mg) or opaque pale grey-coloured cap and body (the cardiovascular polypill 100 mg/20 or 40 mg/ 2.5 mg), imprinted with "AAR 100/20/10", "AAR 100/40/10", "AAR 100/20/5", "AAR 100/40/5", "AAR 100/20/2.5", or "AAR 100/40/2.5". The capsules contain: 2 white or nearly white film-coated tables engraved "AS" of 50 mg of acetylsalicylic acid; 2 greenish-brownish film-coated tablets engraved "AT" of 10 or 20 mg of atorvastatin; 1 pale yellow film-coated tablet engraved "R1", "R5" or "R2" of 10, 5 or 2.5 mg of ramipril, respectively.

Arm title	Control group

Arm description:

Patients assigned to group B continued receiving the usual treatment they were already receiving prior to inclusion in the study, maintaining the time of administration of the medication. When necessary, the patient collected the prescribed treatment at the local pharmacy as per routine clinical practice, according to the characteristics of each country. Patients were instructed not to modify the treatment regimen they had been following prior to their inclusion in the study. Likewise, the patient was

instructed about the need to maintain the same diet and physical activity that he/she had been doing before entering the study.

Arm type	Active comparator
Investigational medicinal product name	Control treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The treatment for cardiovascular prevention considered as optimal by the investigator at patient's enrolment, including acetylsalicylic acid, lipid-lowering agents (statins) and renin-angiotensin-aldosterone system blockers. Pharmaceutical form used for clinical practice.

Number of subjects in period 1[1]	Trinomia group	Control group
Started	218	226
Completed	187	201
Not completed	31	25
Consent withdrawn by subject	4	-
Other	5	3
Adverse events or toxicities	9	2
Concomitant disease	1	-
Lost to follow-up	4	8
Modification of study treatment	3	8
Protocol deviation	5	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 72 patients were excluded because of inspections/audits and 37 for screen failure reasons. Additionally, 2 patients from Trinomia group didn't take medication and were also excluded.

Baseline characteristics

Reporting groups	
Reporting group title	Trinomia group

Reporting group description:

Patients in the Trinomia group incorporated the cardiovascular polypill in their therapeutic strategy. Therefore, patients substituted the angiotensin converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB), statin and acetylsalicylic acid by the cardiovascular polypill. In addition, patients may have taken any other medication that they were taking before.
Replacing the cardiovascular polypill should have been done on the basis that patients were stable and no changes in medication for LDLc and was planned. According to these premises, the doses of atorvastatin (20 or 40 mg) and ramipril (2,5 to 10 mg) were chosen according to the equivalent doses of ARBs/ACEIs and statins that he/she had been taken before entering the study.

Reporting group title	Control group

Reporting group description:

Patients assigned to group B continued receiving the usual treatment they were already receiving prior to inclusion in the study, maintaining the time of administration of the medication. When necessary, the patient collected the prescribed treatment at the local pharmacy as per routine clinical practice, according to the characteristics of each country. Patients were instructed not to modify the treatment regimen they had been following prior to their inclusion in the study. Likewise, the patient was instructed about the need to maintain the same diet and physical activity that he/she had been doing before entering the study.

Reporting group values	Trinomia group	Control group	Total
Number of subjects	218	226	444
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.30	65.97	
standard deviation	± 9.83	± 8.73	-
Gender categorical Units: Subjects			
Female	43	52	95
Male	175	174	349
Race/ethnicity Units: Subjects			
White	217	222	439
African American	1	2	3
Hispanic American	0	1	1
Black	0	1	1
Hypertension Units: Subjects			
Yes	198	210	408
No	18	15	33
Not available	2	1	3
Diabetes Mellitus Units: Subjects			
Type 1	3	1	4
Type 2	77	76	153
No	136	148	284

Not available	2	1	3
Hypercholesterolemia Units: Subjects			
Yes	170	180	350
No	46	45	91
Not available	2	1	3
Hypertriglyceridemia Units: Subjects			
Yes	20	26	46
No	166	185	351
Not available	32	15	47
Chronic renal disease Units: Subjects			
Stage I	0	1	1
Stage II	2	4	6
Stage IIIA	9	8	17
No	202	208	410
Not available	5	5	10
Family history premature cardiovascular events Units: Subjects			
Yes	21	16	37
No	157	166	323
Not available	40	44	84
Alcohol consumption Units: Subjects			
< 4 units per week	31	38	69
4-8 units per week	12	24	36
> 8 units per week	16	24	40
No	129	113	242
Not available	30	27	57
Acute myocardial infarction Units: Subjects			
Yes	83	84	167
No	133	141	274
Not available	2	1	3
Cardiac revascularization with coronary stent Units: Subjects			
Yes	63	74	137
No	153	151	304
Not available	2	1	3
Cardiac revascularization with coronary artery bypass grafting Units: Subjects			
Yes	23	25	48
No	193	200	393
Not available	2	1	3
Stable angina Units: Subjects			
Yes	26	31	57
No	190	194	384

Not available	2	1	3
Ischemic stroke Units: Subjects			
Yes	82	87	169
No	134	138	272
Not available	2	1	3
Extracranial stenosis Units: Subjects			
Yes	19	23	42
No	63	63	126
Not available	136	140	276
Intracranial stenosis Units: Subjects			
Yes	16	13	29
No	66	73	139
Not available	136	140	276
Lacunar infarction Units: Subjects			
Yes	37	44	81
No	45	42	87
Not available	136	140	276
Peripheral artery disease Units: Subjects			
Yes	54	54	108
No	162	171	333
Not available	2	1	3
Antiplatelet and anticoagulant medication: Aspirin Units: Subjects			
Yes	213	225	438
No	3	0	3
Not available	2	1	3
Antiplatelet and anticoagulant medication: Other Units: Subjects			
Yes	42	38	80
No	174	187	361
Not available	2	1	3
Subjects with at least one antiplatelet medication Units: Subjects			
Clopidogrel	24	18	42
Prasugrel	0	1	1
Ticagrelor	7	6	13
Other	6	10	16
None	181	191	372
Subjects with at least one anticoagulant medication Units: Subjects			
Acenocumarol (sintrom)	2	0	2
Rivaroxaban	1	1	2
Other	1	1	2

None	214	224	438
Subjects with at least one medication for dyslipidaemia Units: Subjects			
Yes	216	225	441
Not available	2	1	3
Medication for dyslipidaemia: Atorvastatin Units: Subjects			
Yes	138	148	286
No	80	78	158
Medication for dyslipidaemia: Ezetimibe Units: Subjects			
Yes	23	23	46
No	195	203	398
Medication for dyslipidaemia: Rosuvastatin Units: Subjects			
Yes	47	43	90
No	171	183	354
Medication for dyslipidaemia: Simvastatin Units: Subjects			
Yes	21	27	48
No	197	199	396
Subjects with at least one medication for hypertension Units: Subjects			
Yes	216	225	441
Not available	2	1	3
Medication for hypertension: ACEI-Enalapril Units: Subjects			
Yes	44	33	77
No	174	193	367
Medication for hypertension: ACEI-Ramipril Units: Subjects			
Yes	70	86	156
No	148	140	288
Medication for hypertension: Beta-blockers-Bisoprolol Units: Subjects			
Yes	58	55	113
No	160	171	331
Medication for hypertension: Calcium antagonists-Amlodipine Units: Subjects			
Yes	44	35	79
No	174	191	365
Medication for hypertension: Thiazide diuretics-Hidrochlorothiazide Units: Subjects			
Yes	28	29	57

No	190	197	387
Smoking habits Units: Subjects			
Yes	38	41	79
No	164	178	342
Not available	16	7	23

End points

End points reporting groups

Reporting group title	Trinomia group

Reporting group description:

Patients in the Trinomia group incorporated the cardiovascular polypill in their therapeutic strategy. Therefore, patients substituted the angiotensin converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB), statin and acetylsalicylic acid by the cardiovascular polypill. In addition, patients may have taken any other medication that they were taking before.
Replacing the cardiovascular polypill should have been done on the basis that patients were stable and no changes in medication for LDLc and was planned. According to these premises, the doses of atorvastatin (20 or 40 mg) and ramipril (2,5 to 10 mg) were chosen according to the equivalent doses of ARBs/ACEIs and statins that he/she had been taken before entering the study.

Reporting group title	Control group

Reporting group description:

Patients assigned to group B continued receiving the usual treatment they were already receiving prior to inclusion in the study, maintaining the time of administration of the medication. When necessary, the patient collected the prescribed treatment at the local pharmacy as per routine clinical practice, according to the characteristics of each country. Patients were instructed not to modify the treatment regimen they had been following prior to their inclusion in the study. Likewise, the patient was instructed about the need to maintain the same diet and physical activity that he/she had been doing before entering the study.

Primary: Changes in SBP from baseline to month 6 (mITT)

End point title	Changes in SBP from baseline to month 6 (mITT)

End point description:

The mean ± SD SBP at baseline was 133.80 ± 15.6 mmHg for the Trinomia group and 136.10 ± 16.25 mmHg for the control group. The model-adjusted mean (95% CI) at 6 months was 140.17 (137.97; 142.38) mmHg for the Trinomia group and 136.56 (134.44; 138.69) mmHg for the control group.

End point type	Primary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[1]	193[2]		
Units: mmHg				
arithmetic mean (confidence interval 95%)	5.19 (2.82 to 7.56)	1.40 (-0.88 to 3.69)		

Notes:

[1] - mITT population

[2] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Trinomia group v Control group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0022
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	6.99

Primary: Changes in LDLc from baseline to month 6 (mITT)

End point title	Changes in LDLc from baseline to month 6 (mITT)

End point description:

The mean ± SD LDLc at baseline was 80.20 ± 31.74 mg/dl in the Trinomia group and 83.51 ± 33.90 mg/dl for the control group. The model-adjusted mean (95% CI) at 6 months was 78.80 (75.42; 82.17) mg/dl for the Trinomia group and 80.07 (76.83; 73.32) mg/dl for the control group.

End point type	Primary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[3]	193[4]		
Units: mg/dl				
arithmetic mean (confidence interval 95%)	-3.15 (-6.52 to 0.23)	-1.87 (-5.11 to 1.38)		

Notes:

[3] - mITT population

[4] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5828
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.84
upper limit	3.29

Primary: Changes in SBP from baseline to month 6 (PP)

End point title	Changes in SBP from baseline to month 6 (PP)

End point description:

End point type	Primary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73[5]	111[6]		
Units: mmHg				
arithmetic mean (confidence interval 95%)	7.54 (3.91 to 11.17)	0.94 (-2.10 to 3.99)		

Notes:

[5] - PP population

[6] - PP population

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0044
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.08
upper limit	11.11

Primary: Changes in LDLc from baseline to month 6 (PP)

End point title	Changes in LDLc from baseline to month 6 (PP)

End point description:

End point type	Primary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73[7]	111[8]		
Units: mg /dl				
arithmetic mean (confidence interval 95%)	-1.01 (-6.09 to 4.07)	-2.06 (-6.29 to 2.17)		

Notes:

[7] - PP population

[8] - PP population

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7443
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.29
upper limit	7.38

Primary: Changes in SBP from baseline to month 6 (ITT)

End point title	Changes in SBP from baseline to month 6 (ITT)

End point description:

End point type	Primary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	226		
Units: mmHg				
arithmetic mean (confidence interval 95%)	4.72 (2.42 to 7.02)	1.36 (-0.88 to 3.60)		

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0039
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	6.48

Primary: Changes in LDLc from baseline to month 6 (ITT)

End point title	Changes in LDLc from baseline to month 6 (ITT)

End point description:

End point type	Primary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	226		
Units: mg /dl				
arithmetic mean (confidence interval 95%)	-3.46 (-6.81 to -0.12)	-2.14 (-5.36 to 1.64)		

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5648
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.86
upper limit	3.2

Secondary: Changes in SBP from baseline to month 6 by atherothrombotic cardiovascular disease

End point title	Changes in SBP from baseline to month 6 by atherothrombotic cardiovascular disease

End point description:

Na = number of patients of Trinomia group for each disease. Nb = number of patients of control group for each disease.

End point type	Secondary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[9]	193[10]		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
Coronary artery disease (Na=79; Nb=89)	3.04 (-0.00 to 6.09)	2.90 (0.03 to 5.77)		
Stroke (Na=56; Nb=67)	2.90 (-0.36 to 6.16)	-0.61 (-3.59 to 2.37)		
Peripheral artery disease (Na=39; Nb=37)	9.84 (3.99 to 15.69)	-2.16 (-8.16 to 3.85)		

Notes:

[9] - mITT population

[10] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis (coronary artery disease)
Comparison groups	Trinomia group v Control group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.9459
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.07
upper limit	4.36

Notes:

[11] - Subjects in this analysis: 168

Statistical analysis title	ANCOVA analysis (stroke)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
P-value	= 0.119
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	7.93

Notes:

[12] - Subjects in this analysis: 123

Statistical analysis title	ANCOVA analysis (peripheral artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	= 0.0057
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	12
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.61
upper limit	20.39

Notes:

[13] - Subjects in this analysis: 76

Secondary: Changes in LDLc from baseline to month 6 by atherothrombotic

cardiovascular disease	
End point title	Changes in LDLc from baseline to month 6 by atherothrombotic cardiovascular disease

End point description:

Na = number of patients of Trinomia group for each disease. Nb = number of patients of control group for each disease.

End point type	Secondary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[14]	193[15]		
Units: mg /dl				
arithmetic mean (confidence interval 95%)				
Coronary artery disease (Na=79; Nb=89)	-4.86 (-10.02 to 0.30)	-2.43 (-7.29 to 2.43)		
Stroke (Na=56; Nb=67)	-2.82 (-8.22 to 2.57)	-1.05 (-5.98 to 3.88)		
Peripheral artery disease (Na=39; Nb=37)	-0.10 (-7.40 to 7.21)	-2.12 (-9.63 to 5.38)		

Notes:

[14] - mITT population

[15] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis (coronary artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	= 0.5001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.52
upper limit	4.68

Notes:

[16] - Subjects in this analysis: 168

Statistical analysis title	ANCOVA analysis (stroke)
Comparison groups	Trinomia group v Control group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	= 0.6322
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.09
upper limit	5.54

Notes:

[17] - Subjects in this analysis: 123

Statistical analysis title	ANCOVA analysis (peripheral artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
P-value	= 0.7007
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.45
upper limit	12.5

Notes:

[18] - Subjects in this analysis: 76

Secondary: Evaluation of patients with LDLc and SBP under control according to 2016 European Guidelines

End point title	Evaluation of patients with LDLc and SBP under control according to 2016 European Guidelines

End point description:

End point type	Secondary

End point timeframe:

At month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[19]	193[20]		
Units: patients				
Patients under LDLc control	47	59		
Patients under SBP control	48	65		
Patients under LDLc & SBP control	16	22		

Notes:

[19] - mITT population

[20] - mITT population

Statistical analyses

Statistical analysis title	Fisher's exact test (LDLc)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.423
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	3.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.37
upper limit	12.79

Statistical analysis title	Fisher's exact test (SBP)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.171
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.81
upper limit	15.81

Statistical analysis title	Fisher's exact test (LDLc and SBP)
Comparison groups	Trinomia group v Control group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.352
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	9

Secondary: Evaluation of changes in diastolic blood pressure (DBP)

End point title	Evaluation of changes in diastolic blood pressure (DBP)

End point description:

End point type	Secondary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[21]	193[22]		
Units: mmHg				
arithmetic mean (confidence interval 95%)	0.95 (-0.28 to 2.18)	0.41 (-0.75 to 1.58)		

Notes:

[21] - mITT population

[22] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5338
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	2.23

Secondary: Evaluation of changes in lipid profile

End point title	Evaluation of changes in lipid profile
End point description:	
End point type	Secondary
End point timeframe:	
From baseline to month 6	

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[23]	193[24]		
Units: mg/dl				
arithmetic mean (confidence interval 95%)				
Total Cholesterol	-2.68 (-6.44 to 1.07)	0.27 (-3.30 to 3.84)		
HDLc	0.75 (-0.86 to 2.36)	0.67 (-0.86 to 2.20)		
non-HDLc	-7.01 (-11.18 to -2.84)	-0.71 (-4.58 to 3.17)		
Triglycerides	-5.85 (-12.43 to 0.73)	-0.64 (-6.89 to 5.61)		

Notes:

[23] - mITT population

[24] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis (Total Cholesterol)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2636
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.14
upper limit	2.23

Statistical analysis title	ANCOVA analysis (HDLc)

Comparison groups	Control group v Trinomia group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9421
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.14
upper limit	2.3

Statistical analysis title	ANCOVA analysis (non-HDLc)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0302
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	0.61

Statistical analysis title	ANCOVA analysis (Triglycerides)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2597
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.29
upper limit	3.87

Secondary: Diastolic blood pressure (DBP) by atherothrombotic cardiovascular diseases

End point title	Diastolic blood pressure (DBP) by atherothrombotic cardiovascular diseases

End point description:

Na = number of patients of Trinomia group for each disease. Nb = number of patients of control group for each disease.

End point type	Secondary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[25]	193[26]		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
Coronary artery disease (Na=79; Nb=89)	1.01 (-0.73 to 2.74)	2.12 (0.48 to 3.76)		
Stroke (Na=56; Nb=67)	-1.31 (-3.64 to 1.02)	-0.86 (-2.99 to 1.27)		
Peripheral artery disease (Na=39; Nb=37)	4.10 (1.63 to 6.57)	-1.42 (-3.96 to 1.12)		

Notes:

[25] - mITT population

[26] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis (coronary artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
P-value	= 0.3588
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	1.28

Notes:

[27] - Subjects in this analysis: 168

Statistical analysis title	ANCOVA analysis (stroke)
Comparison groups	Control group v Trinomia group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[28]
P-value	= 0.78
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	2.71

Notes:

[28] - Subjects in this analysis: 123

Statistical analysis title	ANCOVA analysis (peripheral artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[29]
P-value	= 0.0028
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	5.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.97
upper limit	9.07

Notes:

[29] - Subjects in this analysis: 76

Secondary: Total Cholesterol by atherothrombotic cardiovascular diseases

End point title	Total Cholesterol by atherothrombotic cardiovascular diseases

End point description:

Na = number of patients of Trinomia group for each disease. Nb = number of patients of control group for each disease.

End point type	Secondary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[30]	193[31]		
Units: mg/dl				
arithmetic mean (confidence interval 95%)				

Coronary artery disease (Na=79; Nb=89)	-3.74 (-9.58 to 2.10)	1.93 (-3.58 to 7.43)		
Stroke (Na=56; Nb=67)	-3.62 (-9.38 to 2.15)	-1.04 (-6.30 to 4.23)		
Peripheral artery disease (Na=39; Nb=37)	0.60 (-8.43 to 9.62)	-1.13 (-10.40 to 8.13)		

Notes:

[30] - mITT population

[31] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis (coronary artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[32]
P-value	= 0.1659
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.71
upper limit	2.37

Notes:

[32] - Subjects in this analysis:168

Statistical analysis title	ANCOVA analysis (stroke)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[33]
P-value	= 0.5141
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.39
upper limit	5.23

Notes:

[33] - Subjects in this analysis: 76

Statistical analysis title	ANCOVA analysis (peripheral artery disease)
Comparison groups	Trinomia group v Control group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[34]
P-value	= 0.7909
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.22
upper limit	14.67

Notes:

[34] - Subjects in this analysis: 123

Secondary: HDLc by atherothrombotic cardiovascular diseases	
End point title	HDLc by atherothrombotic cardiovascular diseases
End point description:	
Na = number of patients of Trinomia group for each disease. Nb = number of patients of control group for each disease.	
End point type	Secondary
End point timeframe:	
From baseline to month 6	

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[35]	193[36]		
Units: mg/dl				
arithmetic mean (confidence interval 95%)				
Coronary artery disease (Na=79; Nb=89)	0.83 (-0.70 to 2.35)	3.07 (1.64 to 4.51)		
Stroke (Na=56; Nb=67)	0.33 (-2.99 to 3.64)	-2.18 (-5.21 to 0.85)		
Peripheral artery disease (Na=39; Nb=37)	0.74 (-2.77 to 4.25)	0.53 (-3.07 to 4.13)		

Notes:

[35] - mITT population

[36] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis (coronary artery disease)
Comparison groups	Trinomia group v Control group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[37]
P-value	= 0.0353
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.35
upper limit	0.16

Notes:

[37] - Subjects in this analysis: 168

Statistical analysis title	ANCOVA analysis (stroke)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[38]
P-value	= 0.2735
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	7.01

Notes:

[38] - Subjects in this analysis: 123

Statistical analysis title	ANCOVA analysis (peripheral artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[39]
P-value	= 0.9338
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.82
upper limit	5.24

Notes:

[39] - Subjects in this analysis: 76

Secondary: non-HDLc by atherothrombotic cardiovascular diseases

End point title	non-HDLc by atherothrombotic cardiovascular diseases

End point description:

Na = number of patients of Trinomia group for each disease. Nb = number of patients of control group for each disease.

End point type	Secondary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[40]	193[41]		
Units: mg/dl				
arithmetic mean (confidence interval 95%)				
Coronary artery disease (Na=79; Nb=89)	-7.58 (-14.05 to -1.11)	-2.09 (-8.07 to 3.88)		
Stroke (Na=56; Nb=67)	-6.81 (-13.40 to -0.21)	0.20 (-5.79 to 6.18)		
Peripheral artery disease (Na=39; Nb=37)	-5.88 (-15.81 to 4.04)	1.52 (-8.23 to 11.27)		

Notes:

[40] - mITT population

[41] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis (coronary artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[42]
P-value	= 0.2204
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.3
upper limit	3.32

Notes:

[42] - Subjects in this analysis: 168

Statistical analysis title	ANCOVA analysis (stroke)
Comparison groups	Trinomia group v Control group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[43]
P-value	= 0.1225
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.93
upper limit	1.92

Notes:

[43] - Subjects in this analysis: 123

Statistical analysis title	ANCOVA analysis (peripheral artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[44]
P-value	= 0.2906
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.32
upper limit	6.51

Notes:

[44] - Subjects in this analysis: 76

Secondary: Triglycerides by atherothrombotic cardiovascular diseases

End point title	Triglycerides by atherothrombotic cardiovascular diseases

End point description:

Na = number of patients of Trinomia group for each disease. Nb = number of patients of control group for each disease.

End point type	Secondary

End point timeframe:

From baseline to month 6

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[45]	193[46]		
Units: mg/dl				
arithmetic mean (confidence interval 95%)				

Coronary artery disease (Na=79; Nb=89)	-8.35 (-17.60 to 0.90)	-0.44 (-9.15 to 8.28)		
Stroke (Na=56; Nb=67)	-8.52 (-19.58 to 2.54)	-0.71 (-10.83 to 9.40)		
Peripheral artery disease (Na=39; Nb=37)	2.24 (-14.22 to 18.71)	-0.16 (-17.07 to 16.75)		

Notes:

[45] - mITT population

[46] - mITT population

Statistical analyses

Statistical analysis title	ANCOVA analysis (coronary artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[47]
P-value	= 0.2209
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.62
upper limit	4.8

Notes:

[47] - Subjects in this analysis:

Statistical analysis title	ANCOVA analysis (peripheral artery disease)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[48]
P-value	= 0.305
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	7.2

Notes:

[48] - Subjects in this analysis: 123

Statistical analysis title	ANCOVA analysis (peripheral artery disease)
Comparison groups	Trinomia group v Control group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	non-inferiority[49]
P-value	= 0.8403
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.27
upper limit	26.07

Notes:

[49] - Subjects in this analysis: 76

Secondary: Total Score of treatment Satisfaction Questionnaire for medication (TSQM-9)

End point title	Total Score of treatment Satisfaction Questionnaire for medication (TSQM-9)

End point description:

The questions of TSQM-9 refer to three dimensions: effectiveness (questions 1 to 3), convenience (questions 4 to 6) and global satisfaction (questions 7 to 9). In addition to the calculation of the total score for the nine individual questions of TSQM-9, a score can also be calculated for the three dimensions of effectiveness, convenience and global satisfaction. In this calculation also,the total score of the three dimensions can be between 0 and 100. A higher total score equates to greater satisfaction.

End point type	Secondary

End point timeframe:

Throughout the study

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[50]	193[51]		
Units: score				
number (not applicable)				
Efectiveness	69.2	65.3		
Convenience	73.1	65.1		
Global satisfaction	69.1	66.6		

Notes:

[50] - mITT population

[51] - mITT population

Statistical analyses

Statistical analysis title	Mann-Whitney test (effectiveness)
Comparison groups	Control group v Trinomia group

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mann-Whitney test (Convenience)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mann-Whitney test (Global satisfaction)
Comparison groups	Trinomia group v Control group
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0678
Method	Wilcoxon (Mann-Whitney)

Secondary: Ad-hoc questions. How practical is it to take the cardiovascular?	
End point title	Ad-hoc questions. How practical is it to take the cardiovascular?

End point description:

End point type	Secondary

End point timeframe:

Throughout the study

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	193		
Units: patients				
Very practical	139	0		
Relatively practical	25	0		
Relatively unpractical	1	0		
Very unpractical	1	0		
No answer/non-applicable	8	193		

Statistical analyses

No statistical analyses for this end point

Secondary: Ad-hoc questions. Which would you choose?

End point title	Ad-hoc questions. Which would you choose?

End point description:

End point type	Secondary

End point timeframe:

Throughout the study

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	193		
Units: patients				
Cardiovascular polypill	157	0		
3 drugs separately	9	0		
No answer/non-applicable	8	193		

Statistical analyses

No statistical analyses for this end point

Secondary: Ad-hoc questions. Which of the 2 options seems more convenient or practical for you?

End point title	Ad-hoc questions. Which of the 2 options seems more convenient or practical for you?

End point description:

End point type	Secondary

End point timeframe:

throughout the study

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	193		
Units: patients				
Cardiovascular polypill	161	0		
3 drugs separately	5	0		
No answer/ non-applicable	8	193		

Statistical analyses

No statistical analyses for this end point

Secondary: Ad-hoc questions. Which of the 2 options seems the most trustworthy?

End point title	Ad-hoc questions. Which of the 2 options seems the most trustworthy?

End point description:

End point type	Secondary

End point timeframe:

throughout the study

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	193		
Units: patients				
Cardiovascular polypill	148	0		
3 drugs separately	18	0		
No answer/ non-applicable	8	193		

Statistical analyses

No statistical analyses for this end point

Secondary: Ad-hoc questions. Would you switch to the cardiovascular polypill?

End point title	Ad-hoc questions. Would you switch to the cardiovascular polypill?

End point description:

End point type	Secondary

End point timeframe:

throughout the study

End point values	Trinomia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	193		
Units: patients				
Yes, absolutely	0	95		
I would have to think about it	0	59		
No, never	0	11		
I do not know/no reply	0	19		
No answer/ non-applicable	174	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
7 months approximately	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Trisomia group (safety population)
Reporting group description: -	
Reporting group title	Control group (safety population)
Reporting group description: -	

Serious adverse events	Trisomia group (safety population)	Control group (safety population)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 174 (3.45%)	13 / 193 (6.74%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypovolaemic shock			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 174 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Boutonneuse fever			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			

subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trisomia group (safety population)	Control group (safety population)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 174 (25.86%)	35 / 193 (18.13%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Breast cancer			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Polycythaemia vera			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Renal cancer			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Skin papilloma			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Renal cell carcinoma			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 174 (2.30%)	2 / 193 (1.04%)	
occurrences (all)	4	2	
Haematoma			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	

Hypovolaemic shock			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Peripheral ischaemia			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Embolism			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 174 (0.57%)	2 / 193 (1.04%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Illness			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 174 (1.15%)	0 / 193 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	2 / 174 (1.15%)	0 / 193 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Dyspnoea exertional			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Mood altered			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Psychomotor retardation			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 174 (1.15%)	0 / 193 (0.00%)	
occurrences (all)	2	0	
Blood potassium increased			
subjects affected / exposed	2 / 174 (1.15%)	0 / 193 (0.00%)	
occurrences (all)	2	0	
Liver function test abnormal			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	

Limb injury			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 174 (0.00%)	2 / 193 (1.04%)	
occurrences (all)	0	2	
Atrial fibrillation			
subjects affected / exposed	0 / 174 (0.00%)	2 / 193 (1.04%)	
occurrences (all)	0	2	
Ventricular tachycardia			
subjects affected / exposed	0 / 174 (0.00%)	2 / 193 (1.04%)	
occurrences (all)	0	3	
Acute myocardial infarction			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Bundle branch block right			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 174 (1.15%)	0 / 193 (0.00%)	
occurrences (all)	2	0	
Cerebrovascular accident			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Ischaemic stroke			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			

subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Epigastric discomfort			
subjects affected / exposed	2 / 174 (1.15%)	1 / 193 (0.52%)	
occurrences (all)	2	1	
Abdominal discomfort			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Colitis ischaemic			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Xerotic dermatitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Skin disorder			

subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 174 (1.15%)	0 / 193 (0.00%)	
occurrences (all)	2	0	
Renal colic			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Acute kidney injury			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 174 (1.15%)	1 / 193 (0.52%)	
occurrences (all)	2	1	
Neck pain			
subjects affected / exposed	2 / 174 (1.15%)	0 / 193 (0.00%)	
occurrences (all)	2	0	
Groin pain			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 174 (0.00%)	2 / 193 (1.04%)	
occurrences (all)	0	2	
Respiratory tract infection viral			

subjects affected / exposed	2 / 174 (1.15%)	0 / 193 (0.00%)	
occurrences (all)	2	0	
COVID-19			
subjects affected / exposed	0 / 174 (0.00%)	2 / 193 (1.04%)	
occurrences (all)	0	2	
Boutonneuse fever			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Localised infection			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Vestibular neuronitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
COVID-19 pneumonia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Haematoma infection			

subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 174 (0.00%)	1 / 193 (0.52%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 174 (0.00%)	2 / 193 (1.04%)	
occurrences (all)	0	2	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 174 (0.57%)	0 / 193 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2017	Initial submission in Spain. Request of additional information by INFARMED and the EC in Portugal; addition of new exclusion criteria and clarification of Baseline Visit procedures.
22 December 2017	Only for Spain and Ireland. An exclusion criterion is added, the recruitment period is modified, clarifications are added regarding concomitant medication and study treatment. Correction of mistakes.
12 April 2018	Exclusion criteria are added at the request of INFARMED (Portugal) and clarifications of the Baseline visit procedures. Also applied to Spain and Ireland.
15 June 2018	Inclusion of 12 new sites in Portugal.
04 October 2018	Notice to inform study participants on the protection of personal data in Portugal.
11 January 2019	Title adaptation, IMP renaming, rewording of study objectives and endpoints, changes in inclusion/exclusion criteria, addition of new equivalence to ramipril and atorvastatine (inlcuidng the addition of ezetimibe 10 mg or atorvastatin 40 mg for patients taking atorvastatine 80 mg), update and correction of lab test parameters necessary for randomisation, update of statistical methods and non inferiority limit for LDL, changes in the assumptions for the sample size calculations and changes in sample size . Administrative changes.
22 February 2019	Include central laboratory in Ukraine.
28 May 2019	Only for Portugal. New version of the General PIS/ICF (version 2.4, dated 27 August 2019), the PIS/ICF for Pregnancy Follow-up (version 2.4, dated 27 August 2019) and Patient Card (version 1.1, dated 14 May 2019): inclusion of a new site.
01 October 2019	Inclusion of 3 new sites in Portugal.
20 December 2019	Inclusion of 4 new sites in Ireland.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported