Clinical trial results:
A phase III, international, multicenter, randomized and openlabel study to evaluate the efficacy on LDLc and blood pressure reduction and safety of Trinomia® versus usual care in patients with high cardiovascular risk without previous cardiovascular event. The VULCANO trial.

Summary

EudraCT number	2016-004015-13
Trial protocol	ES PT
Global end of trial date	11 December 2019

Results information

Result version number	v1 (current)
This version publication date	02 December 2021
First version publication date	02 December 2021

Trial information

Trial identification

Sponsor protocol code	FMD-TRI-2016-01

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	Diagonal 549 5th floor, Barcelona, Spain, 08029
Public contact	Emili Gil (Medical Director) , Ferrer Internacional, S. A., +34 936003700, egil@ferrer.com
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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	11 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 December 2019
Global end of trial reached?	Yes
Global end of trial date	11 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine, in patients at high or very high cardiovascular risk with no previous event, whether treatment with Trinomia® after a period of 16 weeks is at least non-inferior to the usual treatment alone, in terms of SBP (systolic blood pressure) and c-LDL plasma levels.

Protection of trial subjects:

The information disclosed and obtained during this study was considered confidential and treated as such at all times. The patients included in the study were identified only by a numerical code so that no personal data could be identified the patient collected in the database of the study sponsor. The sponsor, therefore, worked with dissociated data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 445
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Mexico: 55
Worldwide total number of subjects	520
EEA total number of subjects	465

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)	235
From 65 to 84 years	282
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At least the minimum data necessary to confirm the selection criteria (AST/ALT, glomerular filtration, albuminuria and/or proteinuria), and and primary/secondary objectives (LDLc, total cholesterol, HDLc and triglycerides) had to be available in a blood test conducted within the previous 4 weeks.

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

Arm description:

Trinomia: acetylsalicylic acid 100 mg, atorvastatin (20 mg or 40 mg) and ramipril (2.5 mg, 5 mg or 10 mg) administered orally once a day.

Arm type	Experimental
Investigational medicinal product name	Trinomia
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The polypill (acetylsalicylic acid 100 mg, atorvastatin 20 or 40mg and ramipril 2.5, 5 or 10 mg) was administered orally as a single capsule per day

Arm title	Control

Arm description:

The usual treatment that was being prescribed by the patients' doctors, including the different separate drugs that the patients were already receiving before their inclusion in the study.

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

Dosage and administration details:

Patients assigned to control group continued receiving the usual treatment they were already receiving prior to inclusion in the study, maintaining the time of administration of the medication.

Number of subjects in period 1[1]	Trinomia	Control
Started	247	245
Completed	223	236
Not completed	24	9
Consent withdrawn by subject	-	1
Screening failure	-	1
Adverse event, non-fatal	16	3
MG/D	1	-
Error in conversion of baseline medication	1	-
Modification in antihypertensive treatment	1	-
The patient abandons treatment	1	-
Non-compliance of the study procedures	-	1
Change of treatment	1	-
Lost to follow-up	-	3
Protocol deviation	3	-

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: In this study, the ITT data set was the population for the analysis of baseline characteristics, that is, all subjects who received at least one dose of the study treatment after randomisation (n=492). That is why the number of subjects reported to be in the baseline population does not coincide with the worldwide number enrolled in the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Trinomia
Reporting group description:	
Trinomia: acetylsalicylic acid 100 mg, atorvastatin (20 mg or 40 mg) and ramipril (2.5 mg, 5 mg or 10 mg) administered orally once a day.	
Reporting group title	Control
Reporting group description:	
The usual treatment that was being prescribed by the patients' doctors, including the different separate drugs that the patients were already receiving before their inclusion in the study.	

Reporting group values	Trinomia	Control	Total
Number of subjects	247	245	492
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	106	118	224
From 65-84 years	139	126	265
85 years and over	2	1	3
Age continuous Units: years			
arithmetic mean	65.3	64.0	
standard deviation	± 8.3	± 9.1	-
Gender categorical Units: Subjects			
Female	108	95	203
Male	139	150	289
Race Units: Subjects			
Caucasian	221	209	430
Asian	0	2	2
Black	1	2	3
Pure indigenous	24	29	53
Not pure indigenous	1	3	4
Study level Units: Subjects			
No studies	11	15	26
Elementary education	104	91	195
Secondary education	83	74	157
University education	48	64	112
Other	1	1	2
Work situation			

Units: Subjects			
Employed	71	91	162
Unemployed	23	11	34
Retired	146	139	285
Unable/time off	3	2	5
Other	4	2	6
Baseline antiplatelet medication (acetylsalicylic acid) Units: Subjects			
Yes	129	128	257
No	118	117	235
Baseline dyslipidemia medication Units: Subjects			
Yes	247	245	492
No	0	0	0
Baseline hypertension medication Units: Subjects			
Yes	247	245	492
No	0	0	0
Baseline diabetes medication Units: Subjects			
Yes	192	182	374
No	55	63	118
Hypertension Units: Subjects			
Yes	245	245	490
No	2	0	2
Diabetes Units: Subjects			
Yes	195	186	381
No	52	59	111
Hypercholesterolemia Units: Subjects			
Yes	240	235	475
No	7	10	17
Hypertriglyceridemia Units: Subjects			
Yes	46	52	98
No	185	174	359
Missing	16	19	35
Chronic renal failure Units: Subjects			
Yes	33	25	58
No	214	220	434
Family history of heart disease Units: Subjects			
Yes	21	27	48
No	205	200	405
Missing	21	18	39
Smoking habit Units: Subjects			

Yes	32	34	66
No	215	211	426
Treatment with metformine Units: Subjects			
yes	167	161	328
No	80	84	164
Treatment with insulin glargine Units: Subjects			
Yes	36	20	56
No	211	225	436
Treatment with dapagliflozin Units: Subjects			
Yes	32	22	54
No	215	223	438
Treatment with losartan Units: Subjects			
Yes	43	36	79
No	204	209	413
Treatment with hydrochlorothiazide Units: Subjects			
Yes	77	78	155
No	170	167	337
Treatment with enalapril Units: Subjects			
Yes	79	61	140
No	168	184	352
Treatment with amlodipine Units: Subjects			
Yes	52	42	94
No	195	203	398
Treatment with atorvastatin Units: Subjects			
Yes	89	113	202
No	158	132	290
Treatment with simvastatin Units: Subjects			
Yes	98	72	170
No	149	173	322
Smoking years Units: years			
median	36.6	41.0	
standard deviation	± 15.0	± 12.3	-
Cigars per day Units: number of cigars			
median	13.1	19.3	
standard deviation	± 8.5	± 38.9	-
Albumin Units: mg/dL			
arithmetic mean	36.8	15.1	
standard deviation	± 290.0	± 33.3	-
Proteins			

Units: mg/dL			
arithmetic mean	8.8	12.0	
standard deviation	± 27.0	± 36.3	-
Albumin/Creatinine (ratio)			
Units: Ratio			
arithmetic mean	50.2	76.7	
standard deviation	± 108.2	± 226.1	-

Subject analysis sets	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who received at least one dose of the study treatment.	
Subject analysis set title	Modified intention-to-treat
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received at least one dose of the study treatment and have at least one post-baseline primary endpoint measurement.	

Reporting group values	Intention to treat	Modified intention-to-treat	
Number of subjects	492	439	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	224	195	
From 65-84 years	265	241	
85 years and over	3	3	
Age continuous			
Units: years			
arithmetic mean	64.6	64.7	
standard deviation	± 8.7	± 8.9	
Gender categorical			
Units: Subjects			
Female	203	177	
Male	289	262	
Race			
Units: Subjects			
Caucasian	430	382	
Asian	2	1	
Black	3	3	
Pure indigenous	53	50	
Not pure indigenous	4	3	
Study level			
Units: Subjects			

No studies	26	22	
Elementary education	195	174	
Secondary education	117	142	
University education	112	99	
Other	2	2	
Work situation Units: Subjects			
Employed	162	141	
Unemployed	34	28	
Retired	285	259	
Unable/time off	5	5	
Other	6	6	
Baseline antiplatelet medication (acetylsalicylic acid) Units: Subjects			
Yes	257	233	
No	235	206	
Baseline dyslipidemia medication Units: Subjects			
Yes	492	439	
No	0	0	
Baseline hypertension medication Units: Subjects			
Yes	492	439	
No	0	0	
Baseline diabetes medication Units: Subjects			
Yes	374	333	
No	118	106	
Hypertension Units: Subjects			
Yes	490	437	
No	2	2	
Diabetes Units: Subjects			
Yes	381	340	
No	111	99	
Hypercholesterolemia Units: Subjects			
Yes	475	425	
No	17	14	
Hypertriglyceridemia Units: Subjects			
Yes	98	86	
No	359	322	
Missing	35	31	
Chronic renal failure Units: Subjects			
Yes	58	51	
No	434	388	
Family history of heart disease			

Units: Subjects			
Yes	48	39	
No	405	366	
Missing	39	34	
Smoking habit Units: Subjects			
Yes	66	59	
No	426	380	
Treatment with metformine Units: Subjects			
yes	328	294	
No	164	145	
Treatment with insulin glargine Units: Subjects			
Yes	56	47	
No	436	392	
Treatment with dapagliflozin Units: Subjects			
Yes	54	46	
No	438	393	
Treatment with losartan Units: Subjects			
Yes	79	70	
No	413	369	
Treatment with hydrochlorothiazide Units: Subjects			
Yes	155	138	
No	377	301	
Treatment with enalapril Units: Subjects			
Yes	140	131	
No	352	308	
Treatment with amlodipine Units: Subjects			
Yes	94	82	
No	398	357	
Treatment with atorvastatin Units: Subjects			
Yes	202	179	
No	290	260	
Treatment with simvastatin Units: Subjects			
Yes	170	151	
No	322	288	
Smoking years Units: years			
median	38.8	39.1	
standard deviation	± 13.7	± 13.7	
Cigars per day Units: number of cigars			
median	16.3	16.5	

standard deviation	± 28.5	± 30.2	
Albumin Units: mg/dL			
arithmetic mean	26.3	27.1	
standard deviation	± 209.8	± 222.7	
Proteins Units: mg/dL			
arithmetic mean	10.4	9.8	
standard deviation	± 32.0	± 29.5	
Albumin/Creatinine (ratio) Units: Ratio			
arithmetic mean	62.7	63.1	
standard deviation	± 174.4	± 179.0	

End points

End points reporting groups

Reporting group title	Trinomia
Reporting group description:	
Trinomia: acetylsalicylic acid 100 mg, atorvastatin (20 mg or 40 mg) and ramipril (2.5 mg, 5 mg or 10 mg) administered orally once a day.	
Reporting group title	Control
Reporting group description:	
The usual treatment that was being prescribed by the patients' doctors, including the different separate drugs that the patients were already receiving before their inclusion in the study.	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who received at least one dose of the study treatment.	
Subject analysis set title	Modified intention-to-treat
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received at least one dose of the study treatment and have at least one post-baseline primary endpoint measurement.	

Primary: Between-group difference in change in SBP from randomization to 16 weeks

End point title	Between-group difference in change in SBP from randomization to 16 weeks
End point description:	
Primary SBP outcome was analysed in the Modified intent-to-treat (mITT) population.	
End point type	Primary
End point timeframe:	
From randomisation to 16 weeks	

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: mmHg				
arithmetic mean (confidence interval 95%)	1.14 (-0.46 to 2.73)	-0.30 (-1.89 to 1.28)		

Statistical analyses

Statistical analysis title	Primary analysis for non-inferiority
Statistical analysis description:	
To determine whether the treatment with Trinomia is non-inferior to usual care in terms of blood pressure reductions after 16 weeks of follow-up.	
Comparison groups	Trinomia v Control

Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.2099
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.437
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	3.69

Notes:

[1] - The non-inferiority margin of change in SBP was 3

Primary: Between-group difference in change in LDL cholesterol from randomization to 16 weeks

End point title	Between-group difference in change in LDL cholesterol from randomization to 16 weeks

End point description:

Primary LDL cholesterol outcome was analysed in the Modified intent-to-treat (mITT) population.

End point type	Primary

End point timeframe:

From randomisation to week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: mg/dL				
arithmetic mean (confidence interval 95%)	-11.50 (-14.54 to -8.46)	-3.01 (-6.03 to 0.01)		

Statistical analyses

Statistical analysis title	Primary analysis for non-inferiority

Statistical analysis description:

To determine whether the treatment with Trinomia is non-inferior to usual care in terms of LDLc reductions after 16 weeks of follow-up.

Comparison groups	Control v Trinomia
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-8.489

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.78
upper limit	-4.2

Notes:

[2] - The non-inferiority margin of change in LDLc was 10

Secondary: Change in diastolic blood pressure at 16 weeks

End point title	Change in diastolic blood pressure at 16 weeks

End point description:

Secondary DBP outcome was analysed in the Modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

From randomisation to 16 weeks

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: mmHg				
arithmetic mean (confidence interval 95%)	0.12 (-0.88 to 1.11)	-0.54 (-1.53 to 0.45)		

Statistical analyses

Statistical analysis title	Analysis of change in diastolic BP

Statistical analysis description:

The difference between the two treatment arms in the mean change in DBP from randomization to 6 months

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3559
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	2.06

Secondary: Change in total cholesterol at 16 weeks

End point title	Change in total cholesterol at 16 weeks

End point description:

Secondary total cholesterol outcome was analysed in the Modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

From randomisation to 16 weeks

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: mg/dL				
arithmetic mean (confidence interval 95%)	-10.37 (-14.00 to -6.73)	-0.98 (-4.59 to 2.63)		

Statistical analyses

Statistical analysis title	Analysis of change in total cholesterol

Statistical analysis description:

The difference between the two treatment arms in the mean change in total cholesterol from randomization to 6 months

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-9.386
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.52
upper limit	-4.25

Notes:

[3] - Descriptive statistics and two-sided 95% CIs.

Secondary: Change in HDL cholesterol at 16 weeks

End point title	Change in HDL cholesterol at 16 weeks

End point description:

Secondary HDL cholesterol outcome was analysed in the Modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

From randomisation to 16 weeks

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: mg/dL				
arithmetic mean (confidence interval 95%)	-0.47 (-1.97 to 1.03)	-0.76 (-2.25 to 0.73)		

Statistical analyses

Statistical analysis title	Analysis of change in HDL cholesterol

Statistical analysis description:

The difference between the two treatment arms in the mean change in HDLc from randomization to 6 months

Comparison groups	Control v Trinomia
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.7897
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.287
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.826
upper limit	2.399

Notes:

[4] - Descriptive statistics and two-sided 95% CIs.

Secondary: Change in non-HDL cholesterol at 16 weeks

End point title	Change in non-HDL cholesterol at 16 weeks

End point description:

Secondary non-HDL cholesterol outcome was analysed in the Modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

From randomisation to 16 weeks

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: mg/dL				
arithmetic mean (confidence interval 95%)	-10.88 (-14.58 to -7.19)	-2.61 (-6.20 to 0.97)		

Statistical analyses

Statistical analysis title	Analysis of change in non-HDL cholesterol

Statistical analysis description:

The difference between the two treatment arms in the mean change in non-HDL cholesterol from randomization to 6 months

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0017
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-8.269
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.42
upper limit	-3.11

Notes:

[5] - Descriptive statistics and two-sided 95% CIs

Secondary: Change in triglycerides at 16 weeks

End point title	Change in triglycerides at 16 weeks

End point description:

Secondary triglycerides outcome was analysed in the Modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

From randomisation to 16 weeks

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: mg/dL				
arithmetic mean (confidence interval 95%)	-3.97 (-11.39 to 4.58)	0.56 (-7.37 to 8.49)		

Statistical analyses

Statistical analysis title	Analysis of change in triglycerides

Statistical analysis description:

The difference between the two treatment arms in the mean change in triglycerides from randomization to 6 months

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.488
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.22
upper limit	7.28

Notes:

[6] - Descriptive statistics and two-sided 95% CIs

Secondary: Patients with blood pressure control at week 16

End point title	Patients with blood pressure control at week 16

End point description:

Secondary BP control outcome was analysed in the Modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

Week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: Count				
Yes	78	93		
No	140	128		

Statistical analyses

Statistical analysis title	Analysis of blood pressure control at week 16

Statistical analysis description:

The difference between the two treatment arms in the percentage of patients who achieve BP control at 16 weeks

Comparison groups	Trinomia v Control

Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.2057
Method	Fisher exact

Notes:

[7] - Descriptive statistics

Secondary: Patients with LDL control at week 16

End point title	Patients with LDL control at week 16

End point description:

Secondary BP control outcome was analysed in the Modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

Week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: Count				
Yes	82	63		
No	136	158		

Statistical analyses

Statistical analysis title	Analysis of LDL control at week 16

Statistical analysis description:

The difference between the two treatment arms in the percentage of patients who achieve LDL control at 16 weeks

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.054
Method	Fisher exact

Notes:

[8] - Descriptive statistics

Secondary: Maintenance of blood pressure in patients controlled at baseline

End point title	Maintenance of blood pressure in patients controlled at baseline

End point description:

End point type	Secondary

End point timeframe:

From randomisation to week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	83		
Units: Count				
Yes	42	61		
No	28	22		

Statistical analyses

Statistical analysis title	Maintenance of blood pressure control

Statistical analysis description:

To compare between groups the percentage of patients controlled at baseline who maintain BP control of BP at week 16

Comparison groups	Trinomia v Control
Number of subjects included in analysis	153
Analysis specification	Post-hoc
Analysis type	other[9]
P-value	= 0.0864
Method	Fisher exact

Notes:

[9] - Descriptive statistics

Secondary: Maintenance of LDL in patients controlled at baseline

End point title	Maintenance of LDL in patients controlled at baseline

End point description:

End point type	Secondary

End point timeframe:

From randomisation to week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Count				
Yes	38	31		
No	14	20		

Statistical analyses

Statistical analysis title	Maintenance of LDL control

Statistical analysis description:

To compare between groups the percentage of patients controlled at baseline who maintain LDL control of BP at week 16

Comparison groups	Trinomia v Control
Number of subjects included in analysis	103
Analysis specification	Post-hoc
Analysis type	other[10]
P-value	= 0.21
Method	Fisher exact

Notes:

[10] - Descriptive statistics

Secondary: Mean of cardiovascular risk SCORE at 16 weeks

End point title	Mean of cardiovascular risk SCORE at 16 weeks

End point description:

End point type	Secondary

End point timeframe:

Week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: Percentage of risk at 10 years				
arithmetic mean (confidence interval 95%)	5.68 (5.48 to 5.89)	5.93 (5.73 to 6.13)		

Statistical analyses

Statistical analysis title	Between-group difference in CVrisk SCORE at week16

Statistical analysis description:

To evaluate and compare between the two treatment arms the cardiovascular risk SCORE at 10 years, in percent

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.089
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.248

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.04

Notes:

[11] - Descriptive statistics

Secondary: Patients with BP and cLDL control at week 16

End point title	Patients with BP and cLDL control at week 16

End point description:

Secondary BP and cLDL control was analyzed in the Modified Intent-to-Treat (mITT) population

End point type	Secondary

End point timeframe:

Week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: Count				
Yes	33	32		
No	185	189		

Statistical analyses

Statistical analysis title	Analysis of BP and LDL control at week 16

Statistical analysis description:

The difference between the two treatment arms in the percentage of patients who achieve BP and LDC control at 16 weeks

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.8939
Method	Fisher exact

Notes:

[12] - Descriptive statistics

Secondary: Mean of cardiovascular risk PCE at 16 weeks

End point title	Mean of cardiovascular risk PCE at 16 weeks

End point description:

End point type	Secondary

End point timeframe:

Week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: Percentage of risk at 10 years				
arithmetic mean (confidence interval 95%)	23.27 (22.58 to 23.96)	23.96 (23.26 to 24.65)		

Statistical analyses

Statistical analysis title	Between-group difference in CVrisk PCE at week16

Statistical analysis description:

To evaluate and compare between the two treatment arms the cardiovascular risk PCE at 10 years, in percent

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.168
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	0.29

Notes:

[13] - Descriptive statistics

Post-hoc: Cardiovascular risk SCORE at week 16, by categories

End point title	Cardiovascular risk SCORE at week 16, by categories

End point description:

End point type	Post-hoc

End point timeframe:

Week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	168		
Units: Count				
< 1% (Low risk)	25	30		
1-5% (Moderate risk)	75	79		
5-10% (High risk)	45	46		
>10% (Very high risk)	37	33		

Statistical analyses

Statistical analysis title	Analysis of CV risk SCORE by categories

Statistical analysis description:

To compare between the two treatment arms the CV risk SCORE, by categories

Comparison groups	Control v Trinomia
Number of subjects included in analysis	350
Analysis specification	Post-hoc
Analysis type	other[14]
P-value	= 0.434
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - Descriptive statistcs

Post-hoc: Reduction in the CV risk SCORE at week16

End point title	Reduction in the CV risk SCORE at week16

End point description:

End point type	Post-hoc

End point timeframe:

From randomisation to week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	185		
Units: Count				
Yes	15	18		
No	164	167		

Statistical analyses

Statistical analysis title	Reduction in the CV risk SCORE at week 16

Statistical analysis description:

To evaluate and compare between arms the number of patients who reduced the CV risk SCORE at week

16

Comparison groups	Trinomia v Control
Number of subjects included in analysis	364
Analysis specification	Post-hoc
Analysis type	other[15]
P-value	= 0.716
Method	Fisher exact

Notes:
[15] - Descriptive statistics

Post-hoc: Cardiovascular risk PCE at week 16, by categories

End point title	Cardiovascular risk PCE at week 16, by categories

End point description:

End point type	Post-hoc

End point timeframe:
Week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: Count				
< 5% (Low risk)	11	13		
≥ 5%- <7.5% (Moderate risk)	9	10		
≥7.5%-<20% (High risk)	66	66		
≥20% (Very high risk)	99	94		

Statistical analyses

Statistical analysis title	Analysis of CV risk PCE by categories

Statistical analysis description:
To compare between the two treatment arms the CV risk PCE, by categories

Comparison groups	Control v Trinomia
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.6123
Method	Fisher exact

Notes:
[16] - Descriptive statistcs

Post-hoc: Reduction in the CV risk PCE at week 16

End point title	Reduction in the CV risk PCE at week 16

End point description:

End point type	Post-hoc

End point timeframe:

From randomisation to week 16

End point values	Trinomia	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	221		
Units: Count				
Yes	15	11		
No	170	172		

Statistical analyses

Statistical analysis title	Reduction in the CV risk PCE at week 16

Statistical analysis description:

To evaluate and compare between arms the number of patients who reduced the CV risk PCE at week 16

Comparison groups	Trinomia v Control
Number of subjects included in analysis	439
Analysis specification	Post-hoc
Analysis type	other[17]
P-value	= 0.5426
Method	Fisher exact

Notes:

[17] - Descriptive statistics

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization up to 28 days after the End-of Treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Polypill

Reporting group description:

Polypill: acetylsalicylic acid 100 mg, atorvastatin (20 mg or 40 mg) and ramipril (2.5 mg, 5 mg or 10 mg) administered orally once a day.

Reporting group title	Control

Reporting group description:

The usual treatment that was being prescribed by the patients' doctors, including the different separate drugs that the patients were already receiving before their inclusion in the study.

Serious adverse events	Polypill	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 247 (2.43%)	3 / 245 (1.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (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	Polypill	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 247 (25.51%)	47 / 245 (19.18%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Skin papilloma			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Prostate cancer			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 247 (1.21%)	1 / 245 (0.41%)	
occurrences (all)	3	1	
Hypotension			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Blood pressure inadequately controlled			
subjects affected / exposed	3 / 247 (1.21%)	0 / 245 (0.00%)	
occurrences (all)	3	0	
Surgical and medical procedures			
Circumcision			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Transurethral bladder resection			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Tumour excision			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	

Tooth extraction			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Cataract operation			
subjects affected / exposed	2 / 247 (0.81%)	0 / 245 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Polyp			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Prostatism			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Vulvovaginal pruritus			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Aphonia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Catarrh			
subjects affected / exposed	1 / 247 (0.40%)	2 / 245 (0.82%)	
occurrences (all)	1	2	
Cough			
subjects affected / exposed	5 / 247 (2.02%)	0 / 245 (0.00%)	
occurrences (all)	6	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Nervousness			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 247 (0.40%)	3 / 245 (1.22%)	
occurrences (all)	1	3	
Blood creatinine increased			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Blood glucose abnormal			
subjects affected / exposed	3 / 247 (1.21%)	1 / 245 (0.41%)	
occurrences (all)	3	1	
Blood glucose increased			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Blood triglycerides increased			

subjects affected / exposed	1 / 247 (0.40%)	1 / 245 (0.41%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 247 (1.21%)	6 / 245 (2.45%)	
occurrences (all)	3	6	
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Wound dehiscence			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Nervous system disorders			
Sciatica			
subjects affected / exposed	2 / 247 (0.81%)	0 / 245 (0.00%)	
occurrences (all)	2	0	
Dizziness			
subjects affected / exposed	2 / 247 (0.81%)	0 / 245 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Balance disorder			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Cognitive disorder			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Microcytic anaemia			

subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	3 / 247 (1.21%)	2 / 245 (0.82%)	
occurrences (all)	3	3	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Abdominal distension			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 247 (0.40%)	1 / 245 (0.41%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	4 / 247 (1.62%)	0 / 245 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	1 / 247 (0.40%)	1 / 245 (0.41%)	
occurrences (all)	1	1	
Diverticulum			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Dyspepsia			

subjects affected / exposed	2 / 247 (0.81%)	0 / 245 (0.00%)	
occurrences (all)	2	0	
Flatulence			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	2 / 247 (0.81%)	0 / 245 (0.00%)	
occurrences (all)	2	0	
Melaena			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Large intestine polyp			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 247 (0.40%)	1 / 245 (0.41%)	
occurrences (all)	1	1	
Psoriasis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	3 / 247 (1.21%)	1 / 245 (0.41%)	
occurrences (all)	3	1	
Urticaria			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Ecchymosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Lower urinary tract symptoms			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 247 (0.00%)	2 / 245 (0.82%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	4 / 247 (1.62%)	3 / 245 (1.22%)	
occurrences (all)	4	3	
Gouty arthritis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 247 (0.40%)	1 / 245 (0.41%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	3 / 247 (1.21%)	0 / 245 (0.00%)	
occurrences (all)	3	0	
Neck pain			
subjects affected / exposed	1 / 247 (0.40%)	1 / 245 (0.41%)	
occurrences (all)	1	1	
Osteitis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Rheumatoid arthritis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Spinal osteoarthritis			

subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Fibromyalgia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Seronegative arthritis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Muscle contracture			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Balanitis candida			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 247 (0.40%)	2 / 245 (0.82%)	
occurrences (all)	1	2	
Subcutaneous abscess			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	

Tonsillitis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Skin bacterial infection			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Upper respiratory fungal infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Acarodermatitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	3 / 247 (1.21%)	1 / 245 (0.41%)	
occurrences (all)	3	1	
Prostate infection			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	5 / 247 (2.02%)	3 / 245 (1.22%)	
occurrences (all)	5	3	
Onychomycosis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	2 / 247 (0.81%)	1 / 245 (0.41%)	
occurrences (all)	2	1	
Hyperglycaemia			
subjects affected / exposed	2 / 247 (0.81%)	1 / 245 (0.41%)	
occurrences (all)	2	1	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Hyperuricaemia			

subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	2 / 247 (0.81%)	1 / 245 (0.41%)	
occurrences (all)	2	1	
Iron deficiency			
subjects affected / exposed	1 / 247 (0.40%)	0 / 245 (0.00%)	
occurrences (all)	1	0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 247 (0.00%)	1 / 245 (0.41%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2017	▪ The exclusion criteria "Patients with grade III hypertension (blood pressure> 180/110 mmHg) is added. ▪ The information on the criteria for premature withdrawal is expanded. Specifically, it adds "The recommendations of the document-Recommendations related to contraception and pregnancy testing in clinical trials-prepared by the European Clinical Trials Facilitation Group (CTFG) will be followed. ▪ The information is expanded in the definitions section.
02 May 2017	▪ Change in exclusion criteria. ▪ Modification of exclusion criteria. ▪ Modification and inclusion of new information in the criteria for premature withdrawal. ▪ Inclusion of the Benefit-risk analysis section.
15 January 2018	▪ Change the selection period. ▪ Add the time of days in telephone calls. ▪ Update the inclusion and exclusion criteria. ▪ Extend the validity period of a previous analysis from 2 to 4 weeks, and detail the minimum parameters required.
27 July 2018	▪ Change the writing of the study objectives and variables. ▪ Modify inclusion and exclusion criteria. ▪ Add new equivalences of ACE inhibitors, statins and indapamid. ▪ Update / correct analytical parameters necessary for the randomization of patients ▪ Update statistical methods.
08 May 2019	▪ Update monitoring and pharmacovigilance data of the sponsor. ▪ Update equivalences of IECAS and ARAII. ▪ Update non-inferiority limit for LDL from 6% to 10 mg/dl and assumptions of the sample size calculation. ▪ Correction of typographical errors and clarifications in the writing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported