Clinical trial results:
A Multicenter, Randomized, Double-blind, Active-controlled Clinical Trial to Evaluate the Efficacy and Safety of a New Formulation of Zenon (Ezetimibe/Rosuvastatin Fixed Dose Combination) in Patients With Primary Hypercholesterolemia, Not Adequately Controlled on Statin Therapy

Summary

EudraCT number	2016-004556-30
Trial protocol	SK CZ BG IT
Global end of trial date	04 March 2021

Results information

Result version number	v1
This version publication date	13 March 2022
First version publication date	13 March 2022

Trial information

Trial identification

Sponsor protocol code	LPS15021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1202-1326
Other trial identifiers	Study name: ZENON

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis Groupe (SAG)
Sponsor organisation address	54,rue La Boetie, Paris, France, 75008
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	31 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of the fixed dose combination (FDC) rosuvastatin 10 milligrams (mg)/ezetimibe 10 mg (R10/E10) and rosuvastatin 20 mg/ezetimibe 10 mg (R20/E10) compared to up-titration of rosuvastatin 20 mg (R20) and rosuvastatin 40 mg (R40) respectively, and FDC R40/E10 compared to R40 monotherapy, in the reduction of low-density lipoprotein cholesterol (LDL-C) after 6 weeks.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Russian Federation: 176
Country: Number of subjects enrolled	Mexico: 113
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Czechia: 23
Country: Number of subjects enrolled	Slovakia: 28
Country: Number of subjects enrolled	Ukraine: 107
Worldwide total number of subjects	452
EEA total number of subjects	56

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)	320
From 65 to 84 years	132
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 72 active centres (that have screened at least 1 subject) in 7 countries. A total of 1453 subjects were screened from 25 October 2018 to 13 November 2020 of which 758 subjects were screening failures. Subjects entered a 6-week stabilisation run-in period after screening done according to previous statin treatment.

Pre-assignment

Screening details:

High-risk (HR) subjects were randomised in 1:1 ratio to receive either FDC R10/E10, or rosuvastatin 20 mg monotherapy; very high-risk (VHR) subjects were randomised in 1:1:1 to receive either FDC of R20/E10 or R40/E10 or R40 monotherapy. Randomisation was stratified by country.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg

Arm description:

Rosuvastatin 10 mg/Ezetimibe 10 mg (R10/E10) + placebo for Rosuvastatin 20 mg, once daily for 6 weeks in high cardiovascular risk (HR) subjects (LDL-C >=100 milligrams per deciliter [mg/dL] and <=190 mg/dL) (or [2.6- 4.9 millimoles per litre {mmol/L}] at end of run-in phase).

Arm type	Experimental
Investigational medicinal product name	Rosuvastatin 10 mg/Ezetimibe 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin 10 mg/Ezetimibe 10 mg was self-administered by the subject orally once daily for 6 weeks.

Investigational medicinal product name	Placebo to match Rosuvastatin 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Rosuvastatin 20 mg was self-administered by the subject once daily for 6 weeks.

Arm title	High Risk - Rosuvastatin 20 mg

Arm description:

Rosuvastatin 20 mg (R20) + placebo for Rosuvastatin 10 mg/Ezetimibe 10 mg, once daily for 6 weeks in HR subjects (LDL-C >=100 mg/dL and <=190 mg/dL or [2.6- 4.9 mmol/L] at end of run-in phase).

Arm type	Experimental
Investigational medicinal product name	Rosuvastatin 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin 20 mg was self-administered by the subject once daily for 6 weeks.

Investigational medicinal product name	Placebo to match Rosuvastatin 10 mg/Ezetimibe 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Rosuvastatin 10 mg/Ezetimibe 10 mg was self-administered by the subject once daily for 6 weeks.

Arm title	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg

Arm description:

Rosuvastatin 20 mg/Ezetimibe 10 mg (R20/E10) + placebo for Rosuvastatin 40 mg + placebo for Rosuvastatin 40 mg/Ezetimibe 10 mg, once daily for 6 weeks in very high cardiovascular risk (VHR) subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).

Arm type	Experimental
Investigational medicinal product name	Rosuvastatin 20 mg/Ezetimibe 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin 20 mg/Ezetimibe 10 mg was self-administered by the subject orally once daily for 6 weeks.

Investigational medicinal product name	Placebo to match Rosuvastatin 40 mg/Ezetimibe 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Rosuvastatin 40 mg/Ezetimibe 10 mg was self-administered by the subject once daily for 6 weeks.

Investigational medicinal product name	Placebo to match Rosuvastatin 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Rosuvastatin 40 mg was self-administered by the subject once daily for 6 weeks.

Arm title	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg

Arm description:

Rosuvastatin 40 mg/Ezetimibe 10 mg (R40/E10) + placebo for Rosuvastatin 40 mg + placebo for Rosuvastatin 20 mg/Ezetimibe 10 mg, once daily for 6 weeks in VHR subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).

Arm type	Experimental
Investigational medicinal product name	Rosuvastatin 40 mg/Ezetimibe 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin 40 mg/Ezetimibe 10 mg was self-administered by the subject orally once daily for 6 weeks.

Investigational medicinal product name	Placebo to match Rosuvastatin 20 mg/Ezetimibe 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Rosuvastatin 20 mg/Ezetimibe 10 mg was self-administered by the subject once daily for 6 weeks.

Investigational medicinal product name	Placebo to match Rosuvastatin 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Rosuvastatin 40 mg was self-administered by the subject once daily for 6 weeks.

Arm title	Very High Risk - Rosuvastatin 40 mg

Arm description:

Rosuvastatin 40 mg (R40) + placebo for Rosuvastatin 20 mg/Ezetimibe 10 mg + placebo for Rosuvastatin 40 mg/Ezetimibe 10 mg, once daily for 6 weeks in VHR subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).

Arm type	Experimental
Investigational medicinal product name	Rosuvastatin 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin 40 mg was self-administered by the subject once daily for 6 weeks.

Investigational medicinal product name	Placebo to match Rosuvastatin 20 mg/Ezetimibe 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Rosuvastatin 20 mg/Ezetimibe 10 mg was self-administered by the subject once daily for 6 weeks.

Investigational medicinal product name	Placebo to match Rosuvastatin 40 mg/Ezetimibe 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Rosuvastatin 40 mg/Ezetimibe 10 mg was self-administered by the subject once daily for 6 weeks.

Number of subjects in period 1	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg
Started	104	104	82
Completed	104	102	80
Not completed	0	2	2
Adverse event (AE)	-	2	2
Other - unspecified	-	-	-

Number of subjects in period 1	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg
Started	79	83
Completed	75	82
Not completed	4	1
Adverse event (AE)	3	-
Other - unspecified	1	1

Baseline characteristics

Reporting groups	
Reporting group title	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg
Reporting group description:	
Rosuvastatin 10 mg/Ezetimibe 10 mg (R10/E10) + placebo for Rosuvastatin 20 mg, once daily for 6 weeks in high cardiovascular risk (HR) subjects (LDL-C >=100 milligrams per deciliter [mg/dL] and <=190 mg/dL) (or [2.6- 4.9 millimoles per litre {mmol/L}] at end of run-in phase).	
Reporting group title	High Risk - Rosuvastatin 20 mg
Reporting group description:	
Rosuvastatin 20 mg (R20) + placebo for Rosuvastatin 10 mg/Ezetimibe 10 mg, once daily for 6 weeks in HR subjects (LDL-C >=100 mg/dL and <=190 mg/dL or [2.6- 4.9 mmol/L] at end of run-in phase).	
Reporting group title	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg
Reporting group description:	
Rosuvastatin 20 mg/Ezetimibe 10 mg (R20/E10) + placebo for Rosuvastatin 40 mg + placebo for Rosuvastatin 40 mg/Ezetimibe 10 mg, once daily for 6 weeks in very high cardiovascular risk (VHR) subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).	
Reporting group title	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg
Reporting group description:	
Rosuvastatin 40 mg/Ezetimibe 10 mg (R40/E10) + placebo for Rosuvastatin 40 mg + placebo for Rosuvastatin 20 mg/Ezetimibe 10 mg, once daily for 6 weeks in VHR subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).	
Reporting group title	Very High Risk - Rosuvastatin 40 mg
Reporting group description:	
Rosuvastatin 40 mg (R40) + placebo for Rosuvastatin 20 mg/Ezetimibe 10 mg + placebo for Rosuvastatin 40 mg/Ezetimibe 10 mg, once daily for 6 weeks in VHR subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).	

Reporting group values	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg
Number of subjects	104	104	82
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	56.7	57.4	58.9
standard deviation	± 11.10	± 10.06	± 9.81
Gender categorical			
Units: Subjects			
Female	69	62	31
Male	35	42	51
Number of previous statin treatments			
Units: Subjects			
1 statin treatment	104	104	78
2 statin treatments	0	0	4
>2 statin treatments	0	0	0
Prior lipid-modifying therapy (LMT) medications			
Units: Subjects			
R10/R10 Calcium (Ca)	71	73	0
R20/R20 Ca	0	0	46

Atorvastatin/Ca/Ca Trihydrate 40 mg	32	31	0
Atorvastatin/Ca/Ca Trihydrate 80 mg	0	0	36
Simvastatin 80 mg	1	0	0
Duration of hypercholesterolemia			
Units: years			
arithmetic mean	3.8	4.5	5.6
standard deviation	± 4.42	± 5.87	± 4.55
Age of onset of hypercholesterolemia			
Units: years			
arithmetic mean	53.4	53.3	53.7
standard deviation	± 11.41	± 11.51	± 10.40
Duration of previous statin treatment without discontinuation			
Units: years			
arithmetic mean	2.2	1.9	2.9
standard deviation	± 2.72	± 1.76	± 3.62

Reporting group values	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg	Total
Number of subjects	79	83	452
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	62.9	60.8	
standard deviation	± 8.82	± 11.05	-
Gender categorical			
Units: Subjects			
Female	34	41	237
Male	45	42	215
Number of previous statin treatments			
Units: Subjects			
1 statin treatment	77	81	444
2 statin treatments	2	2	8
>2 statin treatments	0	0	0
Prior lipid-modifying therapy (LMT) medications			
Units: Subjects			
R10/R10 Calcium (Ca)	0	0	144
R20/R20 Ca	41	43	130
Atorvastatin/Ca/Ca Trihydrate 40 mg	0	0	63
Atorvastatin/Ca/Ca Trihydrate 80 mg	38	40	114
Simvastatin 80 mg	0	0	1
Duration of hypercholesterolemia			
Units: years			
arithmetic mean	6.4	7.1	
standard deviation	± 6.17	± 5.99	-
Age of onset of hypercholesterolemia			

Units: years			
arithmetic mean	57.0	54.1	
standard deviation	± 9.60	± 10.79	-
Duration of previous statin treatment without discontinuation			
Units: years			
arithmetic mean	2.4	3.3	
standard deviation	± 2.86	± 4.58	-

End points

End points reporting groups

Reporting group title	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg
Reporting group description:	
Rosuvastatin 10 mg/Ezetimibe 10 mg (R10/E10) + placebo for Rosuvastatin 20 mg, once daily for 6 weeks in high cardiovascular risk (HR) subjects (LDL-C >=100 milligrams per deciliter [mg/dL] and <=190 mg/dL) (or [2.6- 4.9 millimoles per litre {mmol/L}] at end of run-in phase).	
Reporting group title	High Risk - Rosuvastatin 20 mg
Reporting group description:	
Rosuvastatin 20 mg (R20) + placebo for Rosuvastatin 10 mg/Ezetimibe 10 mg, once daily for 6 weeks in HR subjects (LDL-C >=100 mg/dL and <=190 mg/dL or [2.6- 4.9 mmol/L] at end of run-in phase).	
Reporting group title	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg
Reporting group description:	
Rosuvastatin 20 mg/Ezetimibe 10 mg (R20/E10) + placebo for Rosuvastatin 40 mg + placebo for Rosuvastatin 40 mg/Ezetimibe 10 mg, once daily for 6 weeks in very high cardiovascular risk (VHR) subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).	
Reporting group title	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg
Reporting group description:	
Rosuvastatin 40 mg/Ezetimibe 10 mg (R40/E10) + placebo for Rosuvastatin 40 mg + placebo for Rosuvastatin 20 mg/Ezetimibe 10 mg, once daily for 6 weeks in VHR subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).	
Reporting group title	Very High Risk - Rosuvastatin 40 mg
Reporting group description:	
Rosuvastatin 40 mg (R40) + placebo for Rosuvastatin 20 mg/Ezetimibe 10 mg + placebo for Rosuvastatin 40 mg/Ezetimibe 10 mg, once daily for 6 weeks in VHR subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).	

Primary: Percent Change from Baseline in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) at Week 6

End point title	Percent Change from Baseline in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) at Week 6
End point description:	
Adjusted least square (LS) means and standard errors (SE) at Week 6 was derived from analyses of covariance (ANCOVA) model with the fixed categorical effect of treatment group, country as well as the continuous fixed covariate of baseline calculated LDL-C value. Analysis was performed on modified intent-to-treat population (mITT) which included all randomised subjects analysed according to the treatment group allocated by randomisation.	
End point type	Primary
End point timeframe:	
Baseline, Week 6	

End point values	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	97	79	78
Units: percent change				
least squares mean (standard error)	-27.02 (±	-21.82 (±	-26.90 (±	-34.28 (±

4.14)	4.25)	3.60)	3.68)

End point values	Very High Risk - Rosuvastatin 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: percent change				
least squares mean (standard error)	-14.62 (± 3.63)			

Statistical analyses

Statistical analysis title	HR: R10/E10 versus R20
Comparison groups	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg v High Risk - Rosuvastatin 20 mg
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306 [1]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.18
upper limit	4.78
Variability estimate	Standard error of the mean
Dispersion value	5.06

Notes:

[1] - Threshold for significance at 0.05 level.

Statistical analysis title	VHR: R40/E10 versus R40
Comparison groups	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-19.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.48
upper limit	-9.84

Variability estimate	Standard error of the mean
Dispersion value	4.98

Notes:

[2] - Threshold for significance at 0.05 level.

Statistical analysis title	VHR: R20/E10 versus R40
Comparison groups	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [3]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-12.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.12
upper limit	-2.44
Variability estimate	Standard error of the mean
Dispersion value	4.99

Notes:

[3] - Threshold for significance at 0.05 level.

Secondary: Percent Change from Baseline in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) at Week 6: Subjects Randomised to R10/E10 and R20/E10

End point title	Percent Change from Baseline in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) at Week 6: Subjects Randomised to R10/E10 and R20/E10[4]

End point description:

Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 6

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is reporting data for applicable arms in the study.

End point values	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	79		
Units: percent change				
arithmetic mean (confidence interval 95%)	-25.03 (-33.89 to -16.17)	-29.25 (-36.84 to -21.65)		

Attachments (see zip file)	Statistical Analysis for Secondary endpoint/Statistical Analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving LDL-C Target at Week 6

End point title	Percentage of Subjects Achieving LDL-C Target at Week 6

End point description:

Percentage of subjects achieving lipid goal levels were defined as: - calculated LDL-C <100 mg/dL (2.6 mmol/L) at Week 6 for HR subjects and calculated LDL-C <70 mg/dL (1.8 mmol/L) at Week 6 for VHR subjects. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 6

End point values	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	97	79	78
Units: percentage of subjects				
number (not applicable)	66.0	55.7	59.5	76.9

End point values	Very High Risk - Rosuvastatin 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: percentage of subjects				
number (not applicable)	41.0			

Statistical analyses

Statistical analysis title	VHR: R40/E10 versus R40

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported for each stratum (HR or VHR). The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

Comparison groups	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.38
upper limit	18.51

Notes:

[5] - Threshold for significance at 0.05 level.

Statistical analysis title	VHR: R20/E10 versus R40

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported for each stratum (HR or VHR). The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

Comparison groups	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.71
upper limit	7.96

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Percent Change from Baseline in Total Cholesterol Levels at Week 6

End point title	Percent Change from Baseline in Total Cholesterol Levels at Week 6

End point description:

Adjusted LS means and standard errors at Week 6 was derived from ANCOVA model including the fixed categorical effects of treatment group, country, as well as the continuous fixed covariate of baseline calculated Total-C value. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	97	79	78
Units: percent change				
least squares mean (standard error)	-17.37 (± 2.66)	-13.71 (± 2.73)	-19.12 (± 2.11)	-22.33 (± 2.15)

End point values	Very High Risk - Rosuvastatin 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: percent change				
least squares mean (standard error)	-8.83 (± 2.13)			

Statistical analyses

Statistical analysis title	VHR: R40/E10 versus R40

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported for each stratum (HR or VHR). The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

Comparison groups	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.26
upper limit	-7.74
Variability estimate	Standard error of the mean
Dispersion value	2.92

Notes:

[7] - Threshold for significance at 0.05 level.

Statistical analysis title	VHR: R20/E10 versus R40

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported for

each stratum (HR or VHR). The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

Comparison groups	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-10.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.04
upper limit	-4.54
Variability estimate	Standard error of the mean
Dispersion value	2.92

Notes:

[8] - Threshold for significance at 0.05 level.

Secondary: Percent Change from Baseline in High-Density Lipoprotein Cholesterol Levels at Week 6

End point title	Percent Change from Baseline in High-Density Lipoprotein Cholesterol Levels at Week 6

End point description:

Adjusted LS means and standard errors at Week 6 was derived from ANCOVA model including the fixed categorical effects of treatment group, country, as well as the continuous fixed covariate of baseline calculated high-density lipoprotein Cholesterol levels. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	97	79	78
Units: percent change				
least squares mean (standard error)	1.25 (± 2.79)	2.10 (± 2.87)	-0.23 (± 1.38)	-2.66 (± 1.41)

End point values	Very High Risk - Rosuvastatin 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: percent change				

least squares mean (standard error)	2.27 (± 1.39)			

Statistical analyses

Statistical analysis title	VHR: R40/E10 versus R40

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported for each stratum (HR or VHR). The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

Comparison groups	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [9]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-4.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.68
upper limit	-1.16
Variability estimate	Standard error of the mean
Dispersion value	1.91

Notes:

[9] - Threshold for significance at 0.05 level.

Statistical analysis title	VHR: R20/E10 versus R40

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported for each stratum (HR or VHR). The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

Comparison groups	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191 [10]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.25
upper limit	1.26

Variability estimate	Standard error of the mean
Dispersion value	1.9

Notes:

[10] - Threshold for significance at 0.05 level.

Secondary: Percent Change from Baseline in Triglycerides Levels at Week 6

End point title	Percent Change from Baseline in Triglycerides Levels at Week 6

End point description:

Adjusted LS means and standard errors at Week 6 was derived from ANCOVA model including the fixed categorical effects of treatment group, country, as well as the continuous fixed covariate of baseline calculated triglycerides levels. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	97	79	78
Units: percent change				
least squares mean (standard error)	-3.62 (± 4.90)	-0.04 (± 5.09)	-10.22 (± 3.69)	-8.54 (± 3.77)

End point values	Very High Risk - Rosuvastatin 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: percent change				
least squares mean (standard error)	-0.70 (± 3.72)			

Statistical analyses

Statistical analysis title	VHR: R40/E10 versus R40

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported for each stratum (HR or VHR). The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

Comparison groups	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128 [11]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-7.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.95
upper limit	2.27
Variability estimate	Standard error of the mean
Dispersion value	5.13

Notes:

[11] - Threshold for significance at 0.05 level.

Statistical analysis title	VHR: R20/E10 versus R40

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported for each stratum (HR or VHR). The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

Comparison groups	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg v Very High Risk - Rosuvastatin 40 mg
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063 [12]
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-9.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.57
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	5.1

Notes:

[12] - Threshold for significance at 0.05 level.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AEs: signing of informed consent up to end of study (i.e., up to 16 weeks). Time frame for treatment emergent AEs: Double Blind (DB) period: intake of first to last dose of DB investigational medicinal product (IMP)+5 days follow up (i.e., up to 8 weeks).

Adverse event reporting additional description:

Reported AEs and deaths were treatment emergent AEs that developed/worsened during 'treatment period' (intake of first to last dose of DB IMP+5 days follow up). Safety population: subjects who received at least one dose of double blind IMP; analysed per treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg

Reporting group description:

Rosuvastatin 10 mg/Ezetimibe 10 mg (R10/E10) + placebo for Rosuvastatin 20 mg, once daily for 6 weeks in high cardiovascular risk (HR) subjects (LDL-C >=100 milligrams per deciliter [mg/dL] and <=190 mg/dL) (or [2.6- 4.9 millimoles per litre {mmol/L}] at end of run-in phase).

Reporting group title	High Risk - Rosuvastatin 20 mg

Reporting group description:

Rosuvastatin 20 mg (R20) + placebo for Rosuvastatin 10 mg/Ezetimibe 10 mg, once daily for 6 weeks in HR subjects (LDL-C >=100 mg/dL and <=190 mg/dL or [2.6- 4.9 mmol/L] at end of run-in phase).

Reporting group title	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg

Reporting group description:

Rosuvastatin 20 mg/Ezetimibe 10 mg (R20/E10) + placebo for Rosuvastatin 40 mg + placebo for Rosuvastatin 40 mg/Ezetimibe 10 mg, once daily for 6 weeks in very high cardiovascular risk (VHR) subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).

Reporting group title	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg

Reporting group description:

Rosuvastatin 40 mg/Ezetimibe 10 mg (R40/E10) + placebo for Rosuvastatin 40 mg + placebo for Rosuvastatin 20 mg/Ezetimibe 10 mg, once daily for 6 weeks in VHR subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).

Reporting group title	Very High Risk - Rosuvastatin 40 mg

Reporting group description:

Rosuvastatin 40 mg (R40) + placebo for Rosuvastatin 20 mg/Ezetimibe 10 mg + placebo for Rosuvastatin 40 mg/Ezetimibe 10 mg, once daily for 6 weeks in VHR subjects (LDL-C >=70 mg/dL and <=160 mg/dL or [1.8- 4.1 mmol/L] at end of run-in phase).

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious AE at the threshold of >5%.

Serious adverse events	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 104 (0.00%)	2 / 104 (1.92%)	1 / 82 (1.22%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			

Femur Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Covid-19			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Chronic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 104 (0.00%)	0 / 104 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 79 (0.00%)	0 / 83 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femur Fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 79 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 79 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 79 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Chronic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 79 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	High Risk - Rosuvastatin 10mg / Ezetimibe 10 mg	High Risk - Rosuvastatin 20 mg	Very High Risk - Rosuvastatin 20 mg / Ezetimibe 10mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 104 (0.00%)	0 / 104 (0.00%)	0 / 82 (0.00%)

Non-serious adverse events	Very High Risk - Rosuvastatin 40 mg / Ezetimibe 10mg	Very High Risk - Rosuvastatin 40 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 79 (0.00%)	0 / 83 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2019	Following changes were made: i) updated the statistical section. Based on study design, inferential approach and/or plans regarding generalisability of the results obtained, all pairwise comparisons did not need to reach statistical significance for a study success. The statistical analysis remained unchanged, only the strategy/interpretation of the results was updated. ii) updated study description to clarify the definition of HR and VHR cardiovascular risk subjects. If Systematic Coronary Risk Evaluation (SCORE) was used as assessment criteria for HR or VHR, the value measured before the starting of LMT was to be taken into consideration. In addition, the definition of screening failure was added. iii) added exclusion criteria to prohibit red yeast rice (RYR) products for at least 6 weeks prior to the Screening Visit and/or plan to take these products before the EOT Visit; it was reported that there was up to a 20% reduction in LDL-C with RYR products at a daily dose of ~2.5-10 mg monacolin (2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the Management of Dyslipidemias). iv) added eGFR <30 mL/min/1.73m^2 and eGFR >=30 and <=59 mL/min/1.73m^2 for VHR subjects as reasons for permanent treatment discontinuation taking into consideration the IMP contraindications and the subjects' profile. v) added definition of AEs of special interest (AESI). Pregnancy occurring in a female partner of a male subject included in the study was added as an AESI. vi) the IMP was to be discontinued only in case of pregnancy occurred in female subject included in the study. vii) changes related to the retaining of the records and the study documents by the Investigators for 25 years after the signature of the final study report. viii) clarified fasting conditions by adding the information that the subjects should not drink anything other than water for 10-12 hours before the blood samples
19 February 2020	Following changes were made: i) amended inclusion criterion to reflect the decrease in the LDL-C lower thresholds at screening for the HR and VHR subjects to allow the recruitment of subjects with better controlled hypercholesterolemia already treated with rosuvastatin that might benefit from the treatment with escalated doses of rosuvastatin or FDC. ii) added an exploratory endpoint in reference to the attaining of the new LDL-C targets, as recommended by the ESC and the EAS 2019 Guidelines for the Management of Dyslipidemias (i.e., an LDL-C reduction of >=50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) for HR subjects and an LDL-C reduction of >=50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) for VHR subjects). iii) aligned the general guidance for the follow-up of laboratory abnormalities and IMP discontinuation in case of alanine aminotransferase or creatine kinase increase with Section 7 "Summary of data and guidance for the Investigator" of the Investigator's Brochure. iv) updated timing of IMP administration to clarify that in the particular situation when the subjects were treated before V2 with statins in the evening, the first run-in rosuvastatin tablet could be taken in the evening. Similarly, in the particular situation when the subjects had taken the run-in rosuvastatin in the evening, the double-blind IMP could be taken in the evening. The Investigator was to instruct the subjects regarding the IMP administration and to report any AE that they might experience.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported